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Halicka, Monika

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The role of neuropsychological changes in the manifestation and treatment of chronic pain

Monika Halicka

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Department of Psychology

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I am the author of this thesis, and the work described therein was carried out by myself personally. Individual chapters are accompanied by an authorship statement indicating my contribution to the work in terms of formulation of ideas, design of methodology, experimental work and presentation of the data in journal format.

Abstract

Chronic pain is a disease of the central nervous system. Neuropsychological symptoms present in some conditions suggest changes in brain function similar to those typically seen in people with brain lesions. One striking example is Complex Regional Pain Syndrome (CRPS), which presents as sensory, motor, and autonomic dysfunctions in the affected body part. People with CRPS can also show distortions in body representation, spatial cognition, and other cognitive functions. These neuropsychological symptoms appear to contribute to the clinical manifestations of CRPS. The role of spatial attention biases was initially suggested by the apparent efficacy of a neurocognitive treatment that targets changes in spatial cognition, called prism adaptation. However, its effects on clinical symptoms of CRPS were only tested in small, uncontrolled studies, and the direct evidence of spatial biases in CRPS is often inconsistent. Thus, our current understanding of the nature and clinical relevance of the neuropsychological symptoms is limited, as is the evidence of the effectiveness of neurocognitive treatments for CRPS. This thesis investigates (1) how neuropsychological functions are altered in CRPS, (2) whether neuropsychological symptoms contribute to the clinical manifestations of CPRS, and (3) whether prism adaptation treatment can reduce pain and other symptoms of CRPS. First, I present a critical literature review, concluding that people with CRPS can present with distorted representation of the affected limb, lateralised biases in spatial cognition, and non-spatially-lateralised cognitive deficits. I further discuss the potential mechanisms of such neuropsychological changes. The experimental studies I present in the following chapters primarily concern the spatial biases. They call into question some of the previous findings about neuropsychological changes in CRPS and their clinical relevance by showing that (a) when a significant spatial bias is observed at individual level, it is not necessarily stable over time, even when pain and body representation are, and (b) when I conducted robust assessments on a large sample, there was no evidence of spatial biases at group level, or of their relationship with clinical symptoms. Finally, I present a randomised controlled trial of prism adaptation treatment for CRPS, which showed no therapeutic effects on pain or CRPS severity beyond those of a control treatment, while overall CRPS severity decreased over time. These results suggest that the previously reported apparent benefits of prism adaptation could be attributed to movement of the affected limb or placebo effect. Overall, this thesis highlights the heterogeneity of neuropsychological symptoms in CRPS, and that previously reported changes in spatial cognition and their clinical relevance might have been overstated. Instead, my findings support the conclusion that motor function and body representation might be associated with clinical manifestation of CRPS and its progression over time. The major contribution of this thesis is providing a detailed and systematic evaluation of neuropsychological changes - especially spatial biases - in CRPS, and a robust test of prism adaptation treatment. The conclusions offer a balanced perspective on the role of neuropsychological functions in the manifestation of CRPS and suggest directions for improved treatments.

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Introduction

In this general introduction, I will describe the concept of pain, considering its primary adaptive functions as well as its pathological manifestation as chronic pain. I will further introduce Complex Regional Pain Syndrome (CRPS), which is the subject of this thesis, and summarise its clinical presentation and proposed mechanisms. Focusing on changes in brain function, I will refer to cortical reorganisation and higher cognitive functions that are altered in chronic pain. I will then summarise generally established relationships between pain and cognition, primarily focusing on attention, and demonstrate how these functions might be affected differently in CRPS. I will provide an overview of cognitive changes found in CRPS, centring on biases in lateralised spatial cognition that resemble hemispatial neglect syndrome. These spatial biases will be the main focus of this thesis. Next, I will summarise currently available treatments for CRPS and their efficacy, and introduce a recently suggested neurocognitive treatment, called prism adaptation, which targets the changes in spatial cognition. This will be followed by a consideration of the proposed mechanisms through which prism adaptation can affect pain and other clinical symptoms of CRPS. Finally, I will provide an outline of the following chapters.

Pain is a common and natural experience, which we regularly encounter in our daily lives in different forms and under varying circumstances. For example, we feel instantaneous pain when we stub our toe on a coffee table, and we can get a headache when working too much on a computer. The International Association for the Study of Pain defines pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey & Bogduk, 1994, p. 209). However, despite its negative connotation, pain serves a crucial and adaptive function to protect our body from harm. In fact, immediate pain typically acts as a warning mechanism, signalling potential injury and facilitating action to minimise impending damage, such as taking our hand off a hot stove. Intense, acute pain can persist with severe injury. However, injury-induced pain also facilitates resting behaviour, for instance, after a surgery, which reduces the chance of worsening the injury and increases the chance of healing. Pain is also a symptom of other diseases (Treede et al., 2019), including mild infections, tissue inflammation, stroke, and cancer. It is therefore not surprising that pain is one of the leading reasons to seek medical advice (Finley et al., 2018; Mäntyselkä et al., 2001). Taken together, pain serves the purpose of signalling that there might be something wrong with our body and that we should alter our behaviour.

In many cases, pain acts as a symptom of some associated tissue damage. Some examples are a needle piercing skin and muscles during injection, a fracture damaging the bones and surrounding soft tissues, or a surgeon cutting through organs during an operation. However, while all these physiological factors can inflict pain, the intensity of perceived pain cannot be considered identical to the severity of tissue damage. This is because pain is a subjective experience and depends on a multitude of physiological and psychological factors. These include our emotional

state, cognitive factors such as attention or expectations, and the sensitivity of our central nervous system (Melzack & Casey, 1968). In fact, pain intensity can be disproportionate to the extent of any injury. One trivial example, which might be familiar to many people, is stepping on a Lego brick. Other examples can be found in the clinical context, for instance, in patients with allodynia, who experience pain evoked by light touch. Furthermore, there are several cases in which we cannot identify any observable physical cause of pain, like in migraine, when pain is experienced in the absence of identifiable damage to tissue or ligaments, or when it is felt even long after an initial injury has healed. In such cases, where pain does not act as a symptom of physical damage, its ongoing manifestation can seem paradoxical. In other words, despite its primarily adaptive function, pain can become pathological in situations when it is not strictly associated with physical injury to the body or persists beyond any adaptive purpose.

Pain that persists beyond the time of normal healing, or for a given length of time based on common medical experience, is defined as chronic. Three months is conventionally used as the point of division between acute and non-malignant chronic pain, however, this definition is arbitrary and the division can vary depending on the type of injury (Merskey & Bogduk, 1994). Chronic pain is an independently acknowledged disease affecting one in five people worldwide (Gureje et al., 1998), although recent estimates in the UK suggest even higher levels of prevalence (Fayaz et al., 2016). In many chronic pain conditions, such as fibromyalgia or non-specific low back pain, pain severity cannot be accounted for by any apparent physical damage or peripheral changes, but rather depends on mechanisms within the central nervous system (hereafter termed "central mechanisms"). Thus, chronic pain has been considered a disorder of the central nervous system, involving plasticity at both the spinal and supraspinal level (for reviews, see Henry, Chiodo, & Yang, 2011; Kuner & Flor, 2017; Lee, Nassikas, & Clauw, 2011; Seifert & Maihöfner, 2008). One such example, which is the central focus of this thesis, is Complex Regional Pain Syndrome (CRPS), and will be described in further detail below.

CRPS is a primarily unilateral chronic pain syndrome that can develop after an injury to a limb. It is associated with spontaneous and evoked pain of a magnitude and duration that is disproportionate to any inciting trauma (Merskey & Bogduk, 1994). The incidence of CRPS is between 6 and 26 in 100 000 people per year (de Mos et al., 2007; Sandroni et al., 2003). A higher incidence was found amongst people who have suffered an injury to a limb, most commonly a fracture, sprain, or surgery (de Mos et al., 2007), although CRPS symptoms can also develop spontaneously (Rooij et al., 2010). Regardless of the type of inciting event, people with CRPS present with disproportionate continuous pain and other sensory, autonomic, and motor symptoms, some of which are illustrated in Figure 1. They can experience innocuous touch as painful, and present with hypersensitivity to pain or loss of sensation in the affected limb. They can show temperature, colour, and sweating asymmetries between the limbs, as well as swelling and changes in the skin, nails, and hair growth in the affected extremity. Motor abnormalities can

involve decreased range of movement, tremor, muscle spasms, dystonia, or weakness (Harden et al., 2010; see Chapter 1 for full diagnostic criteria).

Figure 1. Clinical presentation of CRPS. All photographs illustrate upper limbs of individuals diagnosed with CRPS in their right hand and / or wrist. Examples of apparent CRPS symptoms include: (A) dystrophic changes in the skin, skin colour asymmetry, and muscle weakness (visible atrophy); (B) sweating asymmetry and oedema; (C) oedema, shiny skin, and limited range of movement (inability to open the hand); and (D) dystonia (fingers fixed in unusual posture).

Although CRPS is regional, and thus primarily affects one extremity, its symptomology cannot be explained by peripheral mechanisms alone. There are two types of CRPS that are distinguished based on the presence (type II) or absence (type I) of major peripheral nerve damage, although the clinical symptomatology and diagnostic criteria are the same for both types. While nerve injury is one of the possible causes of CRPS, there is a range of other mechanisms through which CRPS develops. Existing literature indicates that its complex, yet elusive, pathophysiology depends on abnormal interactions between peripheral and central mechanisms. Peripheral processes include inflammation and vasomotor dysfunction, whereas central processes involve neuroplasticity, such as central sensitization (increased responsiveness of spinal neurons, which send nociceptive signals to the cortex even in absence of such input) and cortical reorganisation (for reviews, see Maihofner, Seifert, & Markovic, 2010; Marinus et al., 2011; Reinersmann, Maier, Schwenkreis, & Lenz, 2013). Peripheral inflammatory mechanisms are thought to dominate in the earlier stages of CRPS (up to 6 months after onset), whereas central neuroplasticity is considered the leading pathophysiological mechanism in more chronic stages (Birklein & Schlereth, 2015).

There is evidence that functional reorganisation in the brain, specifically in the primary somatosensory and motor cortices, plays a role in the development and maintenance of similar chronic pain conditions. For instance, in people with phantom limb pain (pain perceived in a limb that has been amputated), the extent of cortical reorganisation was found to strongly correlate with pain intensity (Flor et al., 1995; Karl et al., 2001). Similar relationships were found in individuals with CRPS (Maihofner, Handwerker, Neundorfer, & Birklein, 2003; Pleger et al., 2006) or fibromyalgia, which is a widespread chronic pain condition (Kim et al., 2015). Furthermore, the extent of reorganisation of somatosensory cortical maps was found to increase with disease duration in people with chronic back pain (Flor et al., 1997). However, it should be noted that the relationship between pain and cortical plasticity is still being debated – for instance, high-resolution neuroimaging studies revealed that reorganisation of sensory representations of

the missing hand in amputees with phantom limb pain, and of the affected hand in people with CRPS, might not be as robust as previously reported, and its extent is not necessarily related to pain severity (Makin et al., 2015; Mancini et al., 2019).

Notwithstanding the mixed evidence for cortical reorganisation, CRPS is a particularly vivid example of chronic pain that cannot be explained solely by peripheral pathology. In fact, central neuroplasticity might account for some of the puzzling clinical symptoms of this disorder, such as increased sensitivity to pain that is not limited to the primarily affected part of the body and is present in the areas that do not overlap with the skin areas mainly supplied by single spinal nerves (Rommel et al., 1999). Intriguingly, neuroplasticity also appears to manifest through changes in higher cognitive functions in CRPS and other chronic pain conditions. While cortical representations are based on the neural maps of the areas of the brain dedicated to processing sensory or motor functions, cognitive representations refer to internal mental models of our body and external environment. Altered cognitive representations of the body and external space have been reported in chronic back pain, fibromyalgia, neuropathic pain, phantom limb pain, and other types of pain affecting one limb (Förderreuther et al., 2004; Galer & Jensen, 1999; Kolb et al., 2012; Reinersmann et al., 2010; Bufacchi et al., 2017; Makin et al., 2010; Tsay et al., 2015; Martínez et al., 2018). The assumption that plastic changes in the brain contribute to pain (although the mechanisms for this relationship are unclear) builds the basis for several behavioural treatments that aim to normalise cortical and / or cognitive representations. For example, training of sensory and motor function reversed cortical reorganisation and reduced pain in phantom limb pain and CRPS (Flor et al., 1997; Pleger et al., 2005). Furthermore, neurocognitive rehabilitation methods that target cognitive representations of the painful part of the body, such as mirror visual feedback or graded motor imagery, reduced pain in both phantom limb pain and CRPS (Moseley, 2006; Ramachandran & Altschuler, 2009). Therefore, treatments that target changes in brain function have the potential to reduce clinical manifestations of chronic pain, including CRPS.

Cognitive functions are integral to pain processing, however, their relationship in CRPS appears to be somewhat different than in the context of acute pain and chronic pain more generally. Overall, selective attention, spatial perception, and action selection play a crucial role in protecting the body from potential harm (Legrain & Torta, 2015). The function of these processes is to prioritise the meaningful information that could act as a warning (e.g. pain) and integrate this information with the representations of the body and surrounding space to guide defensive behaviours. The role of selective attention is to prioritise the most significant information. Spatial perception allows locating the painful site or threatening object in space. Action selection prepares the most appropriate motor response to the threat / pain. Locating the potentially threatening information is necessary for identifying the part of the body that could be affected, and to guide a defensive reaction. Thus, coordinating the representations between body and external space is important for pain processing. The relevant regions of space perception can be divided into body

space, based on anatomical coordinates, near space within one's reach and far space beyond one's reach, based on external spatial coordinates (Kerkhoff, 2001; Legrain & Torta, 2015). The spatial location of potentially threatening information is coded based on both anatomical and external coordinates. An example of evidence for this is that crossing the hands over the body midline, which induces incongruence between anatomical and external coordinates, decreases accuracy in the localisation of nociceptive stimuli applied to the hands relative to when the hands are uncrossed (Sambo et al., 2013). Likewise, nociceptive stimulation of one side of the body increases our attention to non-painful information in the corresponding side of near space (Filbrich, Alamia, Blandiaux, et al., 2017). Another example of how pain can affect our spatial attention and representations comes from patients with trigeminal neuralgia: chronic pain affecting one side of the face, in which even a light touch can trigger excruciating pain. The representation of the "painful" side of near space in these patients was found to extend further from their body than the representation of the "non-painful" side, which could reflect increased vigilance to any approaching stimulus that could trigger pain (Bufacchi et al., 2017). Therefore, coordinating body and external representations allows us to locate a potential threat and facilitate action to minimise the damage or avoid exacerbation of pain, for instance, when warding off a wasp, or guarding the painful body part from touch. Examining the relationships between CRPS and these cognitive representations is the central goal of this thesis.

The effects of pain on cognition go beyond the adaptive function to protect the body and can also be detrimental. Up to 20% of patients with chronic pain show clinically significant impairments in working memory, verbal learning and memory, psychomotor speed, and attentional capacity (Hart et al., 2000; Landrø et al., 2013). While all these cognitive functions are, to some extent, considered in this thesis, the main focus lies on attention. Chronic pain has constant interruptive effects on attention that result in an impaired ability to disengage attention from pain (Eccleston & Crombez, 1999). These effects can also manifest as attention bias towards pain-related information which can further exacerbate and maintain pain (although its prevalence in chronic pain has been debated; see Crombez, Van Ryckeghem, Eccleston, & Van Damme, 2013). Thus, deflecting attention away from pain is thought to decrease its perceived intensity (McCaul & Malott, 1984). However, Eccleston (1994) suggested that processing severe pain requires conscious attentional control, and that diverting attention away from pain and towards other tasks might only be possible in the case of low pain intensity.

Taken together, the relationship between pain and cognition appears to be mutual and involve representations of our body, external space, and attentional processes. Pain is attention-grabbing and can bias our processing of bodily and external information, usually towards the pain. However, while these effects have been largely shown in acute pain and chronic pain more generally (i.e., regardless of diagnosis), individuals with CRPS seem to show rather opposite effects of pain-attention interaction. I will discuss these in more detail below.

Higher cognitive changes found in CRPS can affect the perception, representation of, and attention to the CRPS-affected limb and the corresponding side of external space (Galer & Jensen, 1999; Lewis et al., 2007; Moseley et al., 2009; Schwoebel et al., 2001). Throughout the thesis, I will refer to these cognitive changes as neuropsychological symptoms, and their full breadth will be discussed in Chapter 1. In brief, previous research has focused on two main areas of dysfunction: body representation and lateralised spatial cognition. Distortions of body representation include, for example, overestimation of the perceived size of the CRPS-affected limb, altered perception of its shape and weight, poor awareness of its position, reduced sense of ownership of the limb, and difficulties in recognising the laterality of images of limbs corresponding to the affected body part (Lewis et al., 2007, 2010; Moseley, 2005a; Schwoebel et al., 2001). Biases in lateralised spatial cognition are comprised of a deviation of egocentric reference frame (coding of external spatial information in relation to one's own body) towards the CRPS-affected side, reduced attention to the affected relative to the unaffected side, and requiring direct attention to move the affected limb. These biases appear to be linked to the affected limb and / or the side of space in which the affected limb usually resides (Bultitude et al., 2017; Galer et al., 1995; Moseley et al., 2009; Reid et al., 2016, 2018; Sumitani, Shibata, et al., 2007). The evidence for changes in spatial cognition in CRPS remains ambiguous and is one topic of this thesis, however, in general, spatial attention bias is directed away from the affected side and resembles the neurological syndrome called hemispatial neglect.

Hemispatial neglect can follow a brain injury (e.g. a stroke), after which patients show reduced attention to the contralesional, relative to the ipsilesional side of their body and / or space. These attention deficits can affect processing of sensory information, movements, and / or cognitive representations, and they cannot be explained by sensory or motor loss (Kerkhoff, 2001). Biases in spatial cognition found in CRPS are often described through an analogy to hemispatial neglect (Galer et al., 1995; Legrain et al., 2012). While patients with brain lesions neglect the side contralateral to their injured hemisphere, people with CRPS appear to neglect their affected side. Throughout this thesis I will use the term "neglect-like" to describe reduced attention to the affected relative to the unaffected side of the body and space for the purpose of readability and conciseness. However, it is worth noting that there are mechanistic differences between hemispatial neglect and biases in spatial cognition in CRPS. For instance, while cases have been reported where CRPS developed after a stroke (Harrison & Field, 2015), it is typically not associated with brain injury. Furthermore, in contrast to neglect after brain injury, people with CRPS are often aware of some aspects of their attentional deficits, and are able to verbalise them (Frettlöh et al., 2006; Galer & Jensen, 1999). Despite these differences, an extensive body of research on hemispatial neglect provides a robust theoretical and methodological framework to study spatial cognition in CRPS, which, in contrast, has not been extensively studied. This framework substantially informs the hypotheses I put forward and the methods I use in this thesis, including the potential utility of a novel neurocognitive treatment for CRPS.

Current guidelines for CRPS management (Goebel et al., 2018) emphasise an integrated, interdisciplinary approach to reduce pain, restore function, facilitate self-management of the condition, and ultimately improve quality of life. These objectives should be achieved through pain relief medication and procedures, physical and occupational therapy, patient education, and psychological interventions. Pharmacotherapy, in addition to pain relief, also targets inflammation, motor impairment, and loss of bone density. Invasive treatments such as sympathetic nerve blockade or spinal cord stimulation are less common but can provide pain relief for some patients. Physical rehabilitation and behavioural interventions used in clinical practice focus on restoring function and normal perception of the affected limb through exposure therapies, desensitisation, mirror therapy, and graded motor imagery. Self-management education includes advice to direct attention to the affected limb, recognising that patients might "neglect" it. Finally, psychological interventions most often follow principles of cognitive-behavioural therapy (Birklein & Schlereth, 2015; Goebel et al., 2018). A systematic review of randomised controlled trials of treatments for CRPS (Cossins et al., 2013) revealed that there is strong evidence supporting physiotherapy (including graded motor imagery), bisphosphonates (preventing loss of bone density early after CRPS onset), and repetitive transcranial magnetic stimulation. The review further reported moderate evidence for ketamine infusions, and limited evidence for spinal cord stimulation. Nevertheless, for most of the methods used in clinical practice, a lack of robust, randomised controlled trials prevents providing conclusive therapeutic guidelines. Despite the available treatments, the prognosis of recovery from CRPS is relatively poor. Population-based studies revealed that, in usual care, the greatest reduction in symptom severity occurred within the first six months after onset. However, only 5.4% of cases resolved completely within the first 12 months (Bean et al., 2016). Two or more years after onset, 64% of patients still fulfilled the CRPS diagnostic criteria, one third was unable to work, and 16% reported that their symptoms were still worsening (de Mos et al., 2009). Although CRPS primarily affects a distal extremity, such as a hand or a foot, the symptoms might also expand to other limbs over time (Rijn et al., 2011). Moreover, people with a history of CRPS have increased risk of developing CRPS in a second, previously unaffected extremity, when it is subjected to an injury or a surgery (Satteson et al., 2017). Although it is rare, CRPS has a disproportionately high individual and societal cost in terms of quality of life, withdrawal from work and social life, and high burden on the healthcare systems (de Mos et al., 2009; Elsamadicy et al., 2018; van Velzen et al., 2014). Therefore, developing novel treatments holds promise for improving management and outcomes of this debilitating condition. Considering the evidence of cortical reorganisation and neuropsychological symptoms in CRPS, neurocognitive treatments that, in lay terms, aim to "retrain the brain", have potential to reduce pain and improve function through normalising cortical and / or cognitive representations of the body, movement, and the environment.

Prism adaptation is a form of sensory-motor training that has been used to study temporary plasticity in the healthy brain (Redding & Wallace, 1993; von Helmholtz, 1909) and to normalise

spatial attention deficits in hemispatial neglect after brain injury (Rossetti et al., 1998). Typical prism adaptation procedures use prismatic lenses, which refract the light so that the position of an object viewed through such lenses appears shifted to one side of its true location (Figure 2). When we try to quickly reach for that object while wearing prismatic lenses, at first, we miss in the direction of the visual shift. Thus, the actual consequences of our movement do not match the expected consequences. However, this discrepancy diminishes with repeated movement experiences, and after several trials we can accurately reach for the object viewed through prismatic lenses. One process involved in the adjustment of our movements is a strategic online correction of movement trajectory, that is, deliberately mis-pointing further to the side of the perceived object location. Another process involved in the adaptation of our movements to lateral visual shift is a slower but sustained spatial realignment of visual, proprioceptive, and motor reference frames. This spatial realignment is thought to be automatic and not accessible to conscious awareness. The outcomes of this "true" adaptation can be observed as after-effects: once prismatic lenses are removed, and we try to reach for the object again, we miss in the direction opposite to the visual shift (Redding & Wallace, 1993).

Figure 2. A pair of prism goggles and a left hand viewed through a prismatic lens. The left side of the scene has been photographed through a leftward-shifting prismatic lens, thus the objects appear shifted to the left of their true location. The right side of the image represents the scene without any visual distortion.

Research in healthy individuals and people with hemispatial neglect after brain injury shows that the effects of prism adaptation are not limited to lower-level realignment of sensory-motor reference frames (Redding & Wallace, 2006), but also generalise to higher-level cognitive functions, such as spatial attention, mental representations of space, and spatially-defined motor function (Frassinetti et al., 2002; Jacquin-Courtois et al., 2013; Michel, 2016; Striemer & Borza, 2017). In fact, there is robust evidence that two weeks of once- or twice-daily prism adaptation treatment can ameliorate spatial attention deficits after a stroke (Làdavas et al., 2011; Mizuno et al., 2011), and effects can last up to 3 months (Frassinetti et al., 2002; Serino et al., 2007, 2009; Vangkilde & Habekost, 2010). This evidence includes direct comparisons of prism adaptation to sham treatments in randomized controlled trials.

Considering that people with CRPS can present with spatial attention biases resembling hemispatial neglect, and that prism adaptation can effectively reduce attention deficits, this method has been used to treat CRPS, with promising preliminary results (Figure 3). Prism adaptation performed with the affected limb and using lenses that induced visual shifts away from the affected side (thus producing after-effects towards the affected side) significantly reduced pain and other CRPS symptoms in a total of 13 patients with upper-limb CRPS across three independent studies (Bultitude & Rafal, 2010; Christophe, Chabanat, et al., 2016; Sumitani, Rossetti, et al., 2007). Pain reduction was maintained for up to two weeks after treatment cessation (Bultitude & Rafal, 2010; Christophe, Chabanat, et al., 2016). The evidence of the effectiveness of prism adaptation treatment for CRPS, however, is limited, as the abovementioned studies only tested small samples of patients and included neither control treatments nor blinding. Hence, a robust evaluation of the effects of this treatment is required before it can be incorporated into CRPS management.

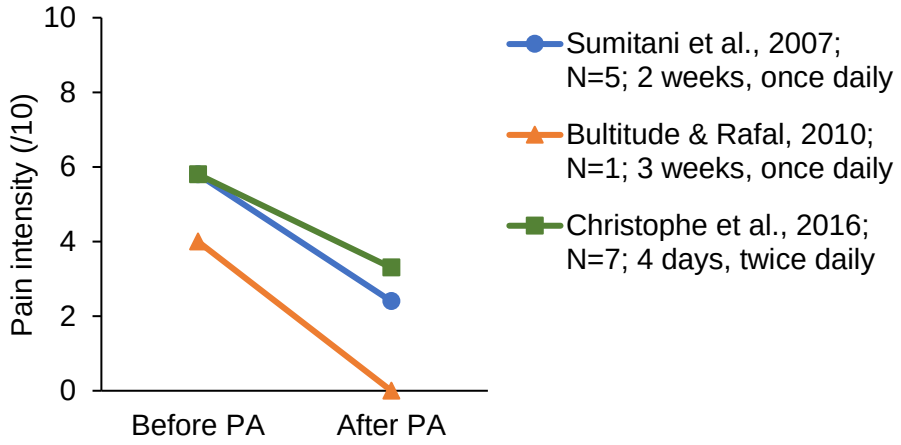

Figure 3. Pain reduction following prism adaptation treatment. The effects of prism adaptation (PA) on pain intensity reported in three previous studies of this treatment in CRPS are summarised. Pain intensity is expressed on an 11-point Numerical Rating Scale: 0 = "no pain at all", 10 = "the worst pain imaginable" used by Sumitani, Rossetti, et al. (2007) and Bultitude and Rafal (2010); average ratings from a 0-100 Visual Analogue Scale with the same anchors used by Christophe, Chabanat, et al. (2016) were scaled for the purpose of comparison with the two former studies.

Another potential limitation to recommending prism adaptation as a standard therapeutic intervention for CRPS is that the mechanisms through which it can reduce pain remain unknown (Torta et al., 2016). The primary mechanism of action is thought to involve normalisation of the spatial attention bias, which is consistent with the initial clinical application of prism adaptation to reduce neglect symptoms after brain injury. This mechanism is supported by the evidence that the effects of prism adaptation generalise across different domains of spatial cognition and motor function in people with and without brain injury (Jacquin-Courtois et al., 2013; Michel, 2016). However, it is unclear how spatial cognition relates to pain. Sumitani, Shibata, et al. (2007) demonstrated that a shift of egocentric reference frame towards the CRPS-affected side was

reversed when they transiently decreased their participants' pain using a nerve blockade in the affected limb. This finding suggests that persistent pain can induce a bias in spatial cognition. Although empirical evidence that CRPS pain *causes* "neglect-like" biases is lacking, one possibility is that habitually directing attention away from pain might serve the purpose of decreasing its perceived intensity (McCaul & Malott, 1984). However, this strategy seems to be maladaptive in the long-term, as the extent of "neglect-like" biases in CRPS has been related to greater severity of pain and other clinical symptoms (Frettlöh et al., 2006; Kolb et al., 2012; Moseley et al., 2009; Moseley, Gallace, & Iannetti, 2012; Reid et al., 2016, 2018; Wittayer et al., 2018). Therefore, increasing attention to the affected side might have therapeutic benefits. Spatial representations were also found to modulate CRPS symptoms. Specifically, Moseley and his colleagues found that limb temperature asymmetry normalised if people with CRPS physically rested the affected limb in the unaffected side of space (Moseley, Gallace, & Iannetti, 2012), or simply viewed it in this location by means of an illusory prismatic shift (Moseley et al., 2013). However, our recent study could not replicate this effect (Vittersø et al., 2020). Direction-specific effects of prism adaptation further support the attentional mechanism of its effects on pain. That is, while prism adaptation inducing after-effects towards the CRPS-affected side (hence increasing attention to that side) was found to reduce pain intensity, inducing after-effects away from the affected side increased pain in one CRPS patient (Sumitani, Rossetti, et al., 2007). Thus, restoring the balance of spatial attention seems to be a key component of the mechanism leading to pain reduction, and this will be the leading hypothesis for this thesis. Nonetheless, there is some evidence speaking against the attentional mechanism. In Christophe, Chabanat, et al.'s (2016) study, prism adaptation significantly reduced pain, without any effect on patients' spatial cognition or motor function. Also, no "neglect-like" symptoms were found in these patients at baseline. Indeed, relationships between "neglect-like" biases and pain intensity in CRPS were not consistently found in several other studies (Bultitude et al., 2017; Filbrich, Alamia, Verfaille, et al., 2017; Michal et al., 2016; Reinersmann et al., 2012).

A potential second mechanism through which prism adaptation could reduce pain is normalisation of sensory-motor integration. It has been suggested that distorted body representation contributes to discrepancies between motor intention and sensory feedback during movement, which can cause pathological pain, similar to how incongruence between visual and vestibular information can induce motion sickness (Bultitude & Rafal, 2010; Harris, 1999; McCabe & Blake, 2008). Although experimental studies in healthy volunteers generally failed to induce painful sensations using sensory-motor conflicts (McCabe et al., 2005; Moseley, 2005c; Moseley & Gandevia, 2005), such manipulations exacerbated pain in people with chronic pain, including CRPS (Brun et al., 2019). Both central and peripheral mechanisms could contribute to persistent discrepancies between motor intention, proprioception, and vision in CRPS. Centrally, they could be driven by cortical reorganisation, distorted body perception, and visuospatial deficits (Bultitude et al., 2017; Di Pietro et al., 2013b, 2013a; Filbrich, Alamia, Verfaille, et al., 2017; Lewis et al., 2007;

Schwoebel et al., 2001; Sumitani, Shibata, et al., 2007). Peripherally, these discrepancies could arise from primary sensory and motor symptoms, and impaired proprioception (Harden et al., 2010; Lewis et al., 2010). The hypothesis that these sensory-motor discrepancies cause (McCabe & Blake, 2008), or rather exacerbate and maintain pain in CRPS, implies that re-establishing sensory-motor congruence could reduce pain. This could relate to the efficacy of prism adaptation because the initial sensory-motor discrepancy during the early phase of prism adaptation could provide a potent error signal that triggers normalisation of body representation and recalibration of distorted sensory and motor representations in people with CRPS. Consistent with this potential sensory-motor mechanism of action, sensory feedback from the affected limb during prism adaptation seems necessary for the therapeutic effects to occur, because performing the treatment with the unaffected limb did not reduce pain in a study of one CRPS patient (Bultitude & Rafal, 2010). Nonetheless, this mechanism does not account for the direction-specific effects of prim adaptation in CRPS, and empirical evidence supporting the sensory-motor model of pain in CRPS is scarce.

The two proposed mechanisms through which prism adaptation could reduce pain, that is normalising spatial attention and sensory-motor integration, are not mutually exclusive. In this thesis, I will examine the evidence for these mechanisms by exploring whether any spatial biases and / or body representation distortions are related to clinical CRPS symptoms, and to any reduction in pain and other symptoms following prism adaptation. Although I will consider both changes in spatial cognition and body representation, my investigations will primarily focus on testing spatial biases, because most inconsistencies in the current CRPS literature occur within this area. Mixed evidence for spatial attention bias in CPRS could be partly due to methodological limitations of the previous studies. In this thesis, I will address these limitations by drawing on the hemispatial neglect literature to create a more appropriate and better-controlled set of tests to measure spatial cognition in CRPS.

In summary, central mechanisms of CRPS involve cortical neuroplasticity that can manifest in neuropsychological symptoms. Some of these symptoms resemble hemispatial neglect after brain injury, although the evidence of the direction and magnitude of biases in spatial cognition in CRPS is not consistent and requires more systematic, robust investigation. Preliminary studies suggested that targeting spatial biases through prism adaptation treatment could provide therapeutic benefits. However, so far there are no sufficiently powered and controlled studies supporting the effectiveness of prism adaptation for CRPS. Furthermore, the working mechanisms of the effects of prism adaptation on pain are poorly understood, and so is the relevance of neuropsychological symptoms for the severity of clinical symptoms of the disorder.

In this thesis, I will focus on the role of neuropsychological changes in the clinical manifestation of CRPS-I, and how understanding them can inform developing more effective treatments for individuals living with this condition. My three overall aims are to investigate (1) how

neuropsychological functions are altered in CRPS, (2) whether neuropsychological symptoms contribute to the clinical manifestations of CPRS, and (3) whether prism adaptation treatment can reduce pain and other symptoms of CRPS.

Chapter 1 provides a conceptual background to the thesis in the form of a comprehensive overview of the current state of research on higher cognitive functions in CRPS. Here I present a review of behavioural evidence of neuropsychological changes in CRPS and discuss the hypothesised mechanisms through which such changes could arise. To this end, I bring together the evidence regarding multiple domains of body representation, lateralised spatial cognition (including "neglect-like" symptoms), and non-spatially lateralised cognitive functions such as object recognition and constructional abilities, numerical processing, working memory, executive functions, and language processing. I further discuss the relevance of neuropsychological changes for clinical signs of CRPS and outline existing treatment approaches that target neuropsychological functions. Integration of the existing evidence of neuropsychological symptoms and their clinical relevance contributes to a better understanding of CRPS as a disorder of the central nervous system. Although the core of this thesis is set around biases in spatial cognition and their relevance for treatment, Chapter 1 contextualises this topic within the full breadth of neuropsychological changes in CRPS and their implications. Through further comparison of cognitive changes in CRPS and other chronic pain syndromes, this chapter demonstrates the potential benefits of studying CRPS as an exemplary condition that can inform us about neuropsychological aspects of other similar syndromes or chronic pain more generally.

Chapter 2 is the first experimental study and investigates under what circumstances spatial biases in CRPS might arise through a longitudinal case study. This allows me to test some of the hypothesised mechanisms proposed in the first chapter. This study follows a woman with CRPS who has previously presented to our laboratory with neglect-like symptoms and body representation disturbance of a severity that is normally only seen in brain-lesioned patients. I assessed her neuropsychological functions over two further sessions with the aim of dissociating the regions of space and sensory modalities in which these biases can manifest. This study provides a proof of concept that 1) people with CRPS can have spatial biases that are apparent on experimental measures of attention such as those that have been developed to test hemispatial neglect after stroke, 2) such biases can change in direction over time (specifically, from a bias *away from* to a bias *towards* the affected side), and 3) the biases can be independent of pain or body representation. So far, no other study has assessed the consistency of neuropsychological symptoms in people with CRPS over long periods of time. Changes in the direction of the spatial bias have potential implications for designing interventions that target neuropsychological symptoms for the treatment of CRPS.

Chapters 3, 4, and 5 describe a double-blind, randomised, controlled trial of a neurocognitive treatment that was first tested on CRPS due to the apparent "neglect-like" component to the

disorder. The purpose of this trial is twofold. First, it aims to robustly test the effects of prism adaptation on clinical symptoms and neuropsychological functions in people with CRPS (Chapter 5). This trial substantially improves upon the methods of the previous studies that provided initial evidence for the effectiveness of prism adaptation treatment by including a large sample of people with CRPS, a control treatment, randomisation, and double-blinding. The secondary aim is to investigate the relationships between the extent of any neuropsychological deviations in people with CRPS (compared to healthy controls) and the severity of clinical symptoms of CRPS (Chapter 4). Understanding which cognitive functions are affected in CRPS could help optimise neurocognitive treatments, for example by identifying how to better tailor the treatments or select individuals for rehabilitation, thus the secondary aim is integral to the study. Another significant contribution of this trial is that it explores two potential working mechanism of prism adaptation, that is, whether it reduces pain through normalising spatial biases and / or body representation in CRPS.

Chapter 3 presents the protocol of the trial, including the rationale, detailed methodology and analysis plan upon which the following two experimental chapters are built.

Chapter 4 reports on the baseline (i.e. pre-treatment) neuropsychological functioning of individuals with CRPS who were recruited into the trial. It comprises a series of experiments assessing a range of neuropsychological functions, including visual spatial attention, mental representation of space, and spatially-defined motor function. In contrast to Chapter 2, which aims to show how spatial cognition *can* be disrupted in CRPS, the purpose of this chapter is to demonstrate what is *typical* of CRPS and reconcile some of the discrepancies in previous literature that are summarised in Chapter 1 by comprehensively testing a large cohort of people with this condition. Drawing from the neglect literature, I composed a battery of computer-based and psychophysical measures of spatial cognition and spatially-defined motor function, which is more comprehensive, sensitive, and better-controlled than in previous research. I examined whether people with CRPS present with systematic spatial biases on these measures compared to healthy control participants. Furthermore, I explored potential relationships between neuropsychological functioning of people with CRPS and the severity of their pain and other CRPS symptoms. Understanding spatial biases and their relevance to clinical symptoms could provide valuable insights into disrupted cognitive functions in CRPS and potential treatment strategies.

Chapter 5 presents the outcomes of the randomised controlled trial of prism adaptation treatment for CRPS. The primary aim of this study is to provide a robust test of the effects of prism adaptation, compared to a control treatment, on pain intensity and CRPS symptoms severity (primary outcomes). To elucidate the mechanisms of any therapeutic benefits, I also examined the effects of prism adaptation on several secondary outcomes. These comprised other clinical signs of the disorder, patients' self-reported CRPS-related and psychological functioning, and neuropsychological functions (including spatial cognition, spatially-defined motor function, and

body representation). Furthermore, to examine how long any benefits of treatment are sustained for, I investigated the time course of any changes on the primary and secondary outcomes in each group, assessed four to six times over the period of 2.5 to 7.5 months. Finally, I explored the potential clinical, self-reported, and neuropsychological predictors of changes in pain and CRPS severity within that time frame, regardless of treatment, to identify possible markers of CRPS progression over time.

Finally, in the general discussion I will summarise the main findings presented in the thesis. I will discuss how these contribute to our understanding of the central mechanisms of CRPS, especially the role of neuropsychological functions in the manifestation and treatment of its clinical symptoms, and what implications can be drawn for other chronic pain conditions.

Chapter 1: Neuropsychological changes in Complex Regional Pain Syndrome (CRPS)

Chapter 1 – Introduction

This chapter presents the current state of knowledge regarding higher cognitive functions in CRPS. Previous findings suggest that people with CRPS can show cognitive deficits resembling hemispatial neglect that is typically caused by brain injury ("neglect-like" symptoms). Through an exhaustive literature review, I provide a comprehensive, critical summary of changes in higher cognitive functions observed in CPRS, demonstrating that they are not limited to "neglect-like" deficits in spatial cognition. The full breadth of neuropsychological symptoms has not been covered in any previous reviews. Yet, integration of the existing evidence is pertinent to understanding the higher-order cognitive processes that might be relevant for the development, maintenance, and treatment of CRPS.

First, this chapter summarises the clinical symptomatology and proposed pathophysiology of CRPS, introducing neuropsychological changes as one aspect of the central mechanisms of the condition. The core of this chapter comprises a review of behavioural evidence of alterations in three cognitive domains: body representation, lateralised spatial cognition, and non-spatially-lateralised cognitive functions. Throughout these three main sections, the findings are integrated within and between each cognitive domain, in an attempt to reconcile any arising inconsistencies by considering potential mechanisms of the neuropsychological changes. This chapter further discusses the clinical relevance of altered cognitive functions and outlines current neurocognitive treatments for CRPS. Although both the theoretical and experimental aspects of this thesis are centred on CRPS, studying this exemplary condition can have implications for understanding other pathological pain syndromes that share similar changes in the central nervous system. Therefore, I briefly refer to neuropsychological changes found in other related disorders. This chapter closes with several concluding remarks and outstanding questions, as well as suggestions of how future research in this field can be improved to further advance our understanding of neuropsychological aspects of CRPS and chronic pain more generally.

Statement of authorship

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Candidate's contribution to the paper (provide details, and also indicate as a percentage)	Monika Halicka considerably contributed to this manuscript (80%), being involved in formulation of ideas (70%), review of the literature (90%), and presentation of material in journal format (90%).		
Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.		
Signed	Monika Halicka	**Date**	10.05.2020

Neuropsychological changes in Complex Regional Pain Syndrome (CRPS)

Monika Halicka[1,2], Axel D. Vittersø[1,2,3], Michael J. Proulx[2,4], and Janet H. Bultitude[1,2]

[1]Centre for Pain Research, University of Bath, Claverton Down Road, Bath BA2 7AY, UK.
[2]Department of Psychology, University of Bath, Claverton Down Road, Bath BA2 7AY, UK.
[3]Department of Sport & Health Sciences, University of Exeter, Prince of Wales Road, Exeter, EX4 4SB, UK.
[4]Centre for Reality & Virtual Environments Augmentation Labs, Department of Computer Science, University of Bath, Claverton Down Road, Bath BA2 7AY, UK.

Correspondence should be addressed to Monika Halicka; m.halicka@bath.ac.uk

Abstract

Complex Regional Pain Syndrome (CRPS) is a poorly understood chronic pain condition of multifactorial origin. CRPS involves sensory, motor, and autonomic symptoms primarily affecting one extremity. Patients can also present with neuropsychological changes such as reduced attention to the CRPS-affected extremity, reminiscent of hemispatial neglect, yet in the absence of any brain lesions. However, this "neglect-like" framework is not sufficient to characterise the range of higher cognitive functions that can be altered in CRPS. This comprehensive literature review synthesises evidence of neuropsychological changes in CRPS in the context of potential central mechanisms of the disorder. The affected neuropsychological functions constitute three distinct, but not independent groups: distorted body representation, deficits in lateralised spatial cognition, and impairment of non-spatially-lateralised higher cognitive functions. We suggest that many of these symptoms appear to be consistent with a broader disruption to parietal function beyond merely what could be considered "neglect-like". Moreover, the extent of neuropsychological symptoms might be related to the clinical signs of CRPS, and rehabilitation methods that target the neuropsychological changes can improve clinical outcomes in CRPS and other chronic pain conditions. Based on the limitations and gaps in the reviewed literature, we provide several suggestions to improve further research on neuropsychological changes in chronic pain.

1. Introduction

Complex Regional Pain Syndrome (CRPS) is a chronic pain condition of poorly understood origin that predominately affects distal parts of one extremity, although in some cases it can spread to other limbs over time [1]. It is characterised by a combination of sensory, motor, and autonomic abnormalities. There is growing body of evidence suggesting that despite the absence of any brain lesions, people with CRPS can present with neuropsychological symptoms. Previous reviews have attempted to address the topic of "neglect-like" symptoms (e.g. spatial attention bias away from the CRPS-affected side [2–4]). Going beyond the analogy to hemispatial neglect and integrating the current knowledge about the full breadth of cognitive changes found in CRPS is important for elucidating the cortical and cognitive mechanisms that could be involved in the development, maintenance, and treatment of its clinical symptoms. This might have implications for other chronic pain conditions that share similar neuropsychological components. Therefore, this article provides a comprehensive, critical review of the evidence for altered neuropsychological functions in CRPS.

We conducted a literature search using the PubMed database for articles including keywords regarding Complex Regional Pain Syndrome published in English between 1995 and 2019. To identify relevant articles, we screened the titles and abstracts for keywords regarding cognitive function. We also manually searched and cross-referenced the reference lists of relevant articles to identify additional studies that were not detected through the initial literature search. Because the clinical presentation and recovery rates of paediatric CRPS differ from CRPS in the adult population [5–7], we limited the scope of this review to adults. However, it is noteworthy that we did not identify any studies investigating neuropsychological changes in children with CRPS in the literature search.

Integrating the existing evidence for neuropsychological changes in CRPS, in the current review we:

- Summarise the clinical presentation of CRPS and proposed pathophysiological mechanisms, including peripheral and central processes, with the aim to situate the neuropsychological symptoms in the clinical picture of the syndrome;
- Review the evidence of neuropsychological changes in CRPS, distinguishing three major categories: body representation disturbances, lateralised spatial cognition deficits, and non-spatially-lateralised higher cognitive deficits. Where applicable, we relate these symptoms to evidence of similar cognitive deficits in people who suffered brain lesions or other chronic pain conditions;
- Discuss the specificity of neuropsychological symptoms to CRPS and their clinical relevance with regard to the development, maintenance, and treatment of CRPS.

We conclude that the currently used "neglect-like" framework is insufficient for characterising the variety of neuropsychological changes shown by people with CRPS, and advocate the role of parietal cortical networks in the emergence of these symptoms.

2. Clinical features and pathophysiology of CRPS

CRPS most commonly develops following a fracture, sprain, or surgery, although there are known instances of spontaneous onset [8–10]. Persistent, continuing pain disproportionate to any preceding injury is the primary complaint, but CRPS also affects a range of other physical and cognitive functions. Below we summarise the clinical manifestations of CRPS and their proposed pathophysiological mechanisms, to provide context for understanding the changes in higher cognitive functions in these patients.

2.1. Sensory, autonomic, and motor symptoms

The diagnosis of CRPS requires both self-reported symptoms and signs that are evident during clinical examination [11] (see diagnostic criteria in Table 1). Sensory changes include perceiving non-noxious stimulation as painful (allodynia) and / or experiencing severe or prolonged pain in response to mildly noxious stimulation (hyperalgesia). Autonomic dysfunction can manifest as temperature, skin colour, and sweating asymmetry between the affected and unaffected limbs, oedema, and changes in skin appearance and hair and nail growth on the affected extremity. Motor abnormalities include tremor, decreased range of movement, muscle weakness, and / or having the affected limb set in a sustained, fixed posture (dystonia). The breadth of clinical manifestations and their possible combinations means that CRPS is a multifaceted and heterogeneous disease.

Table 1 *Budapest diagnostic criteria for CRPS [11,12]*

I.	Continuous pain disproportionate to any inciting event
II.	Reporting at least one symptom in at least three (clinical diagnostic criteria) or four (research diagnostic criteria) categories
III.	Displaying at least one sign at the time of assessment in at least two categories
IV.	Lacking other diagnosis that could better explain the symptoms and signs

Category	**Symptoms / signs**
Sensory	• Hyperesthesia / hyperalgesia • Allodynia
Vasomotor	• Temperature asymmetry • Skin colour changes / asymmetry
Sudomotor / Oedema	• Sweating changes / asymmetry • Oedema
Motor / Trophic	• Decreased range of motion • Motor dysfunction (weakness, tremor, dystonia) • Trophic changes (hair, nails, skin)

2.2. Peripheral and central mechanisms of CRPS

The pathophysiology of CRPS is not well understood and evidence points towards a multifactorial origin of this disorder. The most strongly implicated mechanisms can be classified into peripheral and central processes (for reviews see [13–16]). In brief, an aberrant inflammatory response to tissue trauma can lead to sensitisation of peripheral and spinal nociceptive fibres, neuroinflammation, and dysfunction of peripheral blood circulation [17–20]. Peripheral mechanisms cannot fully account for the fact that CRPS symptoms persist long after the inflammatory response should have resolved. However, patients also show maladaptive plastic changes in the central nervous system [16,21,22]. Changes on the spinal and supraspinal level directly linked to clinical signs of CRPS involve central sensitisation, whereby spinal nociceptive neurons become hyper-responsive to peripheral input and increase nociceptive signalling to the cortex even in absence of such input [23–26]. A shift from inhibition towards facilitation of nociceptive input was also found in the endogenous pain modulation system in CRPS [27]. Peripheral and central mechanisms are not contradictory and they can interact to produce clinical signs of CRPS. Central changes also occur at a higher, cortical level [16,28]. The evidence regarding structural reorganization is scarce [29,30], but extensive evidence of functional cortical reorganization of sensory and motor representations of the limbs in CRPS has been reviewed elsewhere [31,32]. This review concerns behavioural and clinical evidence for altered higher cognitive functions (i.e. neuropsychological symptoms), which thus far have not been comprehensively summarised.

3. Altered neuropsychological functions in CRPS

In the following section, we review higher cognitive processes that are affected in CRPS and that suggest cortical reorganization. The known physiological underpinnings of CRPS alone cannot account for some cognitive phenomena observed in this condition, though neuropsychology provides a useful framework for explaining them. The neuropsychological changes include body representation distortions (section 3.1.), lateralised spatial cognition deficits (section 3.2.), and other neuropsychological symptoms that implicate disruption of broad cortical networks, especially parietal functioning (section 3.3.). We summarise and discuss the study details and behavioural findings from research investigating these neuropsychological changes in CRPS (see also Table 2).

Table 2 *Summary of neuropsychological functions investigated in people with CRPS in research studies published between July 1995 and June 2019*

Neuropsychological function / symptom	Measure / task	Performance of participants with CRPS[a,b]	Study details[c]
Body representation			
Self-reported body perception	Interview	Distorted representation of the affected limb (altered perceptions of size, shape, and weight, desire to amputate, mismatch between sensations and appearance of the limb, erasure of its anatomical parts, poor awareness of its position, asomatognosia)	Galer et al. [33], N=11; Lewis et al. [34], N=27
	Neglect-like symptoms questionnaire [35,36]	Asomatognosia (feelings of foreignness and lack of ownership of the affected limb) (17-90%)	Förderreuther et al. [37], N=40; Frettlöh et al. [35], N=123, PC; Galer and Jensen [36], N=224; Kolb et al. [38], N=20, HC, PC†; Michal et al. [39], N=50, PC; Reinersmann et al. [40], N=24, PC†, [41], N=24, PC; Wittayer et al. [42], N=53
	Bath CRPS Body Perception Disturbance Scale [43]	Distorted representation of the affected limb (see above)	Brun et al. [44], N=13; Bultitude et al. [45], N=24; Kotiuk et al. [46], N=50; Lewis and Schweinhardt [47], N=22, HC; Tajadura-Jiménez et al. [48], N=12
Objective limb size	Estimation of actual limb size based on enlarged or shrunk images	Overestimation of size of the affected limb	Moseley [49], N=50, PC, AL; Peltz et al. [50], N=30, HC, AL
	Tactile distance judgements following tool-use	Perceived lengthening of the unaffected arm and shortening of the affected arm	Vitterso et al. [51], N = 36, HC, BL
Limb position sense	Limb position matching	Reduced accuracy in both limbs	Brun et al. [44], N=13, HC, BL; Lewis et al. [52], N=20, HC, BL
	Manual straight-ahead pointing (eyes closed)	Bias towards the affected side of space	Christophe et al. [53], N=1, NC, BL; Jacquin-Courtois et al. [54], N=1, NC, HC, AL
		Normal	Christophe et al. [55], N=7, NC, BL; Kolb et al. [38], N=20, HC, PC, BL

Neuropsychological function / symptom	**Measure / task**	**Performance of participants with CRPS[a,b]**	**Study details[c]**
Limb movement sense	Estimation of the extent of actual movement relative to altered visual feedback	Reduced accuracy and precision in the affected limb	Brun et al. [44], N=13, HC, AL
Mental limb rotation / internal representation of limbs	Limb laterality recognition test	Reduced accuracy for the affected vs unaffected limb images	Johnson et al. [56], N=29
		Longer reaction times for the affected vs unaffected limb images	Johnson et al. [56], N=29; Moseley [57], N=18, HC; Reid et al. [58], N=130; Schwoebel et al. [59], N=13, HC, [60], N=12
		Longer reaction times for images of both limbs in the affected vs unaffected side of space	Reid et al. [58], N=130
		Longer reaction times for images of both limbs	Bultitude et al. [45], N=24, HC; Kohler et al. [61], N=15, HC; Reinersmann et al. [62], N=12, HC, PC†; Wittayer et al. [42], N=53, HC
		Normal	Breimhorst et al. [63], N=20, HC; Reinersmann et al. [40], N=24, HC, PC
Multisensory integration / body ownership	Rubber hand illusion	Normal	Reinersmann et al. [41], N=24, HC, PC, BL
Bimanual representation of limbs	Artificial finger illusion	Reduced illusion strength for vision-proprioception only (abnormal bimanual representation); normal with tactile input	Wang et al. [64]; N=20, HC, BL
Lateralised spatial cognition			
Self-reported motor neglect	Interview / clinical observation	Motor neglect for the affected limb (slower initiation, execution, and decreased amplitude and spatial extent of movements, required directed attention to move the affected limb, and occurrence of involuntary movements)	Galer et al. [33], N=11

Neuropsychological function / symptom	**Measure / task**	**Performance of participants with CRPS[a,b]**	**Study details[c]**
	Neglect-like symptoms questionnaire [35,36]	Motor neglect for the affected limb (see above) (17-90%)	Frettlöh et al. [35], N=123, PC; Galer and Jensen [36], N=224; Kolb et al. [38], N=20, HC, PC†; Michal et al. [39], N=50, PC; Reinersmann et al. [40], N=24, PC†, [41], N=42, PC; Wittayer et al. [42], N=53
Visuo-motor spatial attention	Line bisection	Bias towards the affected relative to unaffected side of space	Christophe et al. [53], N=1, NC, BL; Jacquin-Courtois et al. [54], N=1, HC, NC, AL; Förderreuther et al. [37], N=29, HC, BL
		Bias away from the affected relative to unaffected side of space	Robinson et al. [65], N=1, NC
		Normal	Christophe et al. [55], N=7, NC, BL; Förderreuther et al. [37], N=29, HC, BL; Kolb et al. [38], N=20, HC, PC; Reid et al. [58], N=13, NC, BL; Reinersmann et al. [40], N=24, HC, PC
	Robot-assisted line bisection	Bias towards the left relative to right side of space	Verfaille et al. [66], N=15, HC, UL
	Line bisection on the limbs	Bias away from the affected relative to unaffected side of space (on the affected limb and on both limbs on the affected side of space)	Reid et al. [58], N=13, NC, BL
	Clock drawing test	Normal	Kolb et al. [38], N=20, HC, PC
Egocentric frame of reference	Visual subjective body midline	Bias towards the affected relative to unaffected side of space (only in the dark)	Christophe et al. [53], N=1, NC; Jacquin-Courtois et al. [54], N=1, HC, NC; Sumitani et al. [67], N=27, HC [68], N=36, HC, [69], N=5, NC; Uematsu et al. [70], N=22, PC
		Bias towards the left relative to right side of space (in the dark)	Reinersmann et al. [40], N=24, HC, PC
		Normal (in the dark)	Christophe et al. [55], N=7, NC; Wittayer et al. [42], N=53, HC

Neuropsychological function / symptom	**Measure / task**	**Performance of participants with CRPS[a,b]**	**Study details[c]**
Tactile spatial attention	Confrontation test (detection of concurrent stimulation on both limbs)	Omissions of stimuli on the affected side of the body (extinction; 14%)	Cohen et al. [71], N=22, BL
	Temporal Order Judgements	Bias away from the affected relative to unaffected limb (when tactile stimuli delivered to uncrossed hands)	Reid et al. [58], N=13, NC
	Temporal Order Judgements	Bias away from the affected limb (when tactile stimuli delivered to uncrossed hands) and from the affected side of space (when tactile stimuli delivered to hands crossed over body midline), relative to the unaffected limb and side of space	Moseley et al. [72], N=10, [73], N=10, HC
		Normal (crossed and uncrossed hands)	Filbrich et al. [74], N=12, NC
Auditory spatial attention	Temporal Order Judgements	Normal	Reid et al. [58], N=13, NC
Visual spatial attention	Temporal Order Judgements	Bias away from the affected relative to unaffected side of space and limb (when visual stimuli presented in near space without hands, or on the surface of uncrossed hands, but not when hands were crossed over body midline)	Bultitude et al. [45], N=24, HC
		Bias away from the affected relative to unaffected side of space (when visual stimuli presented near uncrossed hands, but not far from the hands)	Filbrich et al. [74], N=14, NC
	Orienting saccades to cued and non-cued stimuli in the left and right visual fields	Normal	Filippopulos et al. [75], N=8, HC
	Speeded detection task	Longer reaction times in the right side of space	Kolb et al. [38], N=20, HC, PC
Internal representation of space	Mental number line bisection	Deviation away from the affected relative to unaffected side of space	Sumitani et al. [67], N=27, HC

Neuropsychological function / symptom	Measure / task	Performance of participants with CRPS[a,b]	Study details[c]
		Deviation towards the affected relative to unaffected side of space	Christophe et al. [53], N=1, NC; Jacquin-Courtois et al. [54], N=1, NC, HC
Spatially-defined motor control	Rhythmic finger tapping	Normal / no hands asymmetry (with one and both hands, in uncrossed and crossed posture, with and without visual feedback)	Christophe et al. [55], N=7, HC, BL
		Normal / no hands asymmetry (with one and both hands, hands close together or further apart, without visual feedback)	Christophe et al. [53], N=1, BL
	Speeded button pressing	Slower and more variable movements (with the affected vs unaffected hand in both sides of space, and with both hands in the affected vs unaffected side of space)	Reid et al. [76], N=13, BL
	Circle drawing task	Reduced accuracy (with the affected vs unaffected hand in both sides of space, and with both hands in the affected vs unaffected side of space)	Reid et al. [76], N=13, BL
		Normal / no hands asymmetry	Christophe et al. [55], N=7, HC, BL
Non-spatially-lateralised cognition			
Object recognition	Tactile recognition of objects	Astereognosia for the affected hand (64%)	Cohen et al. [71], N=22, HC, BL
	Visual recognition of objects	Normal	Robinson et al. [65], N=1, NC
Face recognition	Benton Test of Face Perception	Prosopagnosia	Robinson et al. [65], N=1, NC
Finger identification	Identification of indicated fingers (verbally, by touch, pointing, or movement)	Finger agnosia on the affected limb (48-59%); longer reaction times, reduced accuracy, and increased variability of finger discrimination (on both hands, but worse on the affected hand)	Cohen et al. [71], N=22, HC, BL; Förderreuther et al. [37], N=73, BL; Kuttikat et al. [77], N=13, HC, BL
		Normal	Robinson et al. [65], N=1, NC, UL
Tactile recognition of writing on the skin	Identification of letters and numbers traced onto one's palm	Dysgraphaesthesia on the affected hand (36%)	Cohen et al. [71], N=22, HC, BL

Neuropsychological function / symptom	**Measure / task**	**Performance of participants with CRPS[a,b]**	**Study details[c]**
Constructional ability	Copying or constructing named geometric figures using drawing or matchsticks	Constructional apraxia for the affected hand (32%)	Cohen et al. [71], N=22, HC, BL
	Kohs Block test	Normal	Kolb et al. [38], N=20, HC, PC
Numerical and language processing	Counting, mental arithmetic, reading, repeating, writing, copying, identifying numbers and letters / words, spelling	Dyscalculia (27%); dysgraphia for the affected hand (27%)	Cohen et al. [71], N=22, HC, BL
Speech repetition	Repetition of words and sentences, confrontation naming	Conductional dysphasia (4%)	Cohen et al. [71], N=22, HC
Verbal fluency	Boston Naming test, animal (semantic) fluency, letter fluency	Impaired verbal fluency	Libon et al. [78], N=137, NC
Visuo-spatial orientation	Rod Orientation test	Normal	Kolb et al. [38], N=20, HC, PC
Knowledge about object orientation	Object orientation judgements, copying, drawing, reorienting objects into upright position	Agnosia for object orientation	Robinson et al. [65], N=1, NC
Knowledge about order and orientation of numbers and letters / words	Spontaneous and dictated writing, copying	Mirror-reversal in writing and reading; horizontal inversion of letters and words, and letters and numbers ordering in writing (cases for the affected hand, both hands, and unaffected hand)	Cohen et al. [71], N=22, HC, BL; Robinson et al. [65], N=1, UL
	Letter orientation recognition	Normal (for standard vs reflected letters, and left vs right side of space)	Reid et al. [58], N=13
Body sides differentiation	Identification of indicated body parts (verbally, by touch, or pointing)	Left-right disorientation (9%)	Cohen et al. [71], N=22, HC, BL
		Normal	Robinson et al. [65], N=1, NC, UL

Neuropsychological function / symptom	**Measure / task**	**Performance of participants with CRPS[a,b]**	**Study details[c]**
Imitation of complex movements	Pantomime of indicated motor acts	Ideomotor apraxia (5%)	Cohen et al. [71], N=22, HC, BL
Temporal acuity	Temporal Order Judgements	Reduced temporal acuity	Bultitude et al. [45], N=24, HC
Alertness	Test of Attentional Performance	Normal response readiness	Reinersmann et al. [62], N=12; HC, PC
Working memory	Digit span	Impaired working memory span	Libon et al. [78], N=137, NC
	Test of Attentional Performance	Normal continuous updating	Reinersmann et al. [62], N=12, HC, PC
Spatial working memory	Block Tapping test	Normal	Kolb et al. [38], N=20, HC, PC, Right Limb
Episodic verbal memory and learning	California Verbal Learning test II	Impaired encoding, recall, and recognition	Libon et al. [78], N=137, NC
Global cognitive processing	Digit Span, Boston Naming test, animal (semantic) fluency, letter fluency, California Verbal Learning test II	Global processing impairment (particularly impaired naming, declarative memory, executive function; 23%) or mild dysexecutive syndrome (particularly impaired working memory and verbal fluency; 42%)	Libon et al. [78], N=137, NC

[a]Percentages represent the proportion of individuals with CRPS out of the total CRPS sample who presented with abnormal performance. We reported percentages where available; in other cases, we presented group effects.

[b]Normal performance indicates that there were no differences between participants with CRPS and control participants, and / or between the affected and unaffected side among participants with CRPS.

[c]N represents CRPS sample size. Where applicable, we specified which control group was included (HC = healthy / pain-free controls; PC = pain controls; NC = normative data or comparison against zero; † = no significant difference between CRPS and control group), and which limb(s) were tested (AL = affected limb; UL = unaffected limb; BL = both limbs).

3.1. Body representation

Altered body representation is among the earliest and best characterised neuropsychological changes in CRPS. Cognitive representations of one's body are derived from proprioceptive, vestibular, somatosensory, and visual information that interact with the motor system to guide actions [79]. This dynamic online representation of body posture is often called "body schema" [80]. However, in this review we use a broader term "body representation" that also incorporates the structural definition of the body (i.e., perception of its size, shape, and boundaries) as well as the body image (defined as the semantic representation of the names and function of distinct body parts) [80]. Distortions of body representation manifest in CRPS as self-reported disturbed perceptions, ownership of and feelings towards the affected limb; difficulties with mentally rotating and recognising the laterality of pictures of the limbs; and erroneous estimation of the

size, position, and movement of the limbs from single sensory modalities (while multisensory integration appears intact). Below we discuss evidence for each of these manifestations in turn.

3.1.1. Self-reported body perception disturbances

Initial clinical reports [33] and questionnaire studies [36,37] showed that up to 60% of patients reported loss of ownership, recognition, or awareness of their CRPS-affected limb. This research aimed to measure so-called "neglect-like" symptoms in CRPS. Neglect is an attention deficit affecting the hemispace contralateral to a brain lesion [81], discussed in more detail in section 3.2. (see also Table 3). Early research in CRPS considered reports of the affected limb not being part of the patient's body and feeling dead as "cognitive neglect" symptoms [35,36], yet we would argue that they are better characterised as a disturbance of the mental representation of the body. Specifically, these symptoms closely resemble asomatognosia (lost sense of ownership of one's limb), which can follow temporo-parietal lesions. Asomatognosia often co-occurs with hemispatial neglect, yet it is not a diagnostic feature of the neglect syndrome [82,83]. Interviews of people with CRPS about their perceptions of their body [34] revealed a range of disturbances consistent with distorted body representation (see also [52]). These included perceptions of the affected limb as being larger or smaller, misshapen, or heavier relative to its true size, shape, and weight; negative feelings towards the affected limb such as disgust or hatred (reminiscent of misoplegia [84]); the desire to amputate it; a mismatch between sensation of the affected limb and its appearance; lacking parts of the limb from their mental representation; and poor awareness of the affected limb's position. Although more prevalent in chronic CRPS [37], such experiences can manifest within days of disease onset [34]. The severity of self-reported body perception disturbance correlated with impaired tactile acuity [47], which was linked to reorganization of the primary and secondary cortical maps of the CRPS-affected limb [85,86]. This suggests that subjective body representation distortion could be accompanied by changes in the brain pertaining to the central mechanisms of CRPS.

3.1.2. Limb laterality recognition

Several studies have used variations of the limb laterality recognition task, also sometimes referred to as mental hand / foot rotation, to measure body schema in CRPS (e.g. [45,57–59,61–63]). In a typical procedure, the task requires speeded identification of left or right limbs from pictures of hands or feet in different postures and / or at different angles of rotation from the upright (canonical) position. In pain-free controls, response times increase with the angle of rotation (i.e., they get longer consistent with the spatial disparity between the pictures of limbs and the canonical posture, and also according to the biomechanical constraints that make some hand rotations physically easier than others [87]). Therefore, it is thought that the limb laterality recognition task involves mentally rotating the pictured limb to match it to the current position of one's own limb (or vice versa) in a manner that complies with biomechanical constraints [59,88,89]. This is thought to require the participants to use the cognitive representations of the

limb that corresponds to the one depicted in the picture [90,91]. Consistent with the involvement of motor imagery [87], neuroimaging studies show increased activation of premotor and parietal regions during hand laterality recognition [92,93].

People with CRPS were less accurate and slower in determining the laterality of images corresponding to their painful limb than of images corresponding to their unaffected limb [56–60], indicative of the cognitive representation of the affected limb being distorted. Moreover, Reid et al. [58] found that in addition to taking longer to recognise pictures of limbs corresponding to their affected side of the body, people with CRPS took longer to recognise pictures of limbs presented in their affected side of space. The latter effect occurred for both the images of hands and feet regardless of whether participants had CRPS in upper or lower limbs, however, it was specific to images of body parts, and not to other stimuli (e.g. letters). Although there appears to be strong evidence for lateralised body representation distortions in CRPS, some authors have reported equally slowed limb laterality judgements for pictures representing both the affected and unaffected limbs, compared to healthy controls [42,45,61,62]. This could be due to methodological differences, or it could indicate more generalised changes in body representation, or reduced psychomotor speed due to the effects of pain medication [94] or chronic pain in general (rather than CRPS specifically) [95]. This would be consistent with the finding of comparable slowing in laterality recognition of both limbs in phantom limb pain and CRPS [45,62]. Finally, there are also contradictory findings suggesting that both people with CRPS and healthy controls are faster in recognising the images of limbs corresponding to their dominant hand, regardless of which side of the body is affected [40], or do not differ in limb laterality recognition [63].

3.1.3. Estimation of limb size, position, and movement from unisensory cues

Distorted perceptions of the body are evident in several modalities, including its visual and proprioceptive representations. Patients with CRPS were presented with compressed and expanded schematic drawings of hands [50] and real pictures of their own hands manipulated in the same manner [49]. When asked to indicate the pictures that most accurately represented the size of their affected hands, they tended to choose enlarged images, overestimating the size of their painful extremities.

Distorted estimates of limb position and limb movement have also been reported for people with CRPS. “Manual” or “proprioceptive straight-ahead” [96] requires participants to point straight ahead of their perceived body midline, without vision of the limb or external space (e.g. with the eyes closed), and thus relies on integrating proprioceptive information about position of an arm with perceived body midline. A shift of manual straight-ahead towards the affected side of space relative to objective midline has been found in a case of CRPS [53,54] when the patient used the affected hand, and also when she used the unaffected one. Nevertheless, two group studies found no significant deviations from the true body midline, nor from the subjective midline of healthy and pain controls, on the same manual task performed with either or both arms [38,55]. Manual

straight-ahead estimations of individuals with CRPS were not more variable than among the controls [38]. However, people with CRPS presented with impaired limb position sense in two studies that used matching tasks. In Lewis et al.'s [52] study, participants were required to match the position of their affected and unaffected arm to specified targets that were *external* to their to their body (i.e. point their arms as though they were the hour hand on a clock showing a particular time). In Brun et al.'s [44] study, they were required to match the position of the affected or unaffected arm to the mirror-reverse position of their other arm, which had been passively moved by a robot. In both of these studies, people with CRPS made more errors and were less precise than healthy controls when positioning both arms when they did not have vision of their limbs. This suggests that proprioceptive deficits are bilateral and thus cannot be attributed solely to sensory deficits in the CRPS-affected limb.

In a third task, people with CRPS also presented with reduced accuracy and precision in the sense of limb *movement*. Participants observed movement of a virtual limb anchored to the movement of their unseen affected limb and judged whether it was smaller or greater than their actual movement. People with CRPS both under- and overestimated the extent of their movements relative to healthy controls [44]. Both this impaired sense of movement of the affected limb, and the previous findings of more variable positioning performance for the affected and unaffected limbs, provide evidence of impaired proprioception, since participants could not see their limbs and thus were forced to rely on proprioception for these tasks [44,52–54]. However, these deficits are not consistently found [38,55].

3.1.4. Multisensory contributions to body representation in CRPS

Research also investigated how information from multiple sensory modalities is combined to contribute to body representation in CRPS. An additional observation from the study by Lewis et al. [52] is that when people with CRPS kept their eyes open while they placed their affected arm at particular clock face locations, their limb position deficits were smaller than when they performed the task with their eyes closed. Positioning of the unaffected arm did not significantly improve with vision. This demonstrates that people with CRPS rely on visual cues in addition to proprioceptive ones when estimating the position of the affected limb. Furthermore, Tajadura-Jiménez et al. [48] found that the self-reported inability to visualize the affected limb or overestimation of its size could be altered by auditory feedback during movement. In this study, people with upper or lower limb CRPS heard manipulated sounds linked to their footsteps, with higher frequencies inducing an impression of lighter body weight and smaller body dimensions, and lower frequencies inducing an impression of heavier weight and larger body dimensions. Similar to the performance of healthy participants in another study [97] the gait of people with CRPS was altered in that the time of foot contact with the floor increased with lower-frequency sounds, consistent with having heavier body. For some participants, the sound feedback also helped to restore the representations of previously missing parts of their body. The studies of

Lewis et al. [52] and Tajadura-Jiménez et al. [48] suggest that people with CRPS can integrate visual and auditory feedback with proprioceptive information from their body into the body representation.

However, the process of updating body representation might differ for the affected and the unaffected side. In a recent study, Vittersø et al. [51] demonstrated altered updating of body representation following tool use for people with CRPS compared to controls. Participants estimated the felt distance between two points touching the arm before and after tool use. Tool use typically leads to a shortening of the felt distance between the two points, which is interpreted as a perceived lengthening of the arms as the body representation is updated to incorporate the tools. Relative to pain-free controls, people with upper limb CRPS had a more pronounced updating of body representation for their unaffected arm following tool use (i.e. a larger perceived lengthening than the controls), and showed the opposite pattern for their affected arm (i.e. a perceived shortening). These findings suggest that the representation of the body is more malleable for people with CRPS, and that multisensory information can have different effects for the affected and unaffected limb.

Susceptibility to body-related multisensory illusions can provide insights into which mechanisms governing body representation might be disrupted or preserved in CRPS. The rubber hand illusion is a phenomenon thought to indicate that body ownership arises from integrating congruent visual and tactile input with the existing mental representation of one's body [98]. Thus, preserved multisensory integration should be necessary for illusory ownership of the rubber hand to occur. During the rubber hand illusion, a participant views a real-size rubber arm placed where their real arm would normally reside, while their real arm is placed out of sight nearby and in an analogous orientation [98]. The experimenter applies tactile stimulation (e.g. strokes from paintbrushes) to the rubber and real hand synchronously. There are three classic measures of successful induction of the rubber hand illusion - subjective ownership of the rubber hand; skin conductance responses to viewing the rubber hand being harmed; and a proprioceptive drift of the felt position of the real hand towards the position of the rubber hand. In a study that used the first two of these measures, Reinersmann et al. [41] demonstrated that people with CRPS were able to experience this illusion normally both when the affected and unaffected limbs were stimulated. Specifically, their subjective ownership of the rubber hand and skin conductance responses were not significantly different from those of people with other types of upper limb pain and pain-free controls [41]. We can draw two main conclusions from these findings: that people with CRPS can experience an illusory ownership of an artificial limb, and that they have intact multisensory integration.

Successful induction of rubber hand illusion [41] showed that people with CRPS have the normal ability to perceive an illusory ownership of an artificial body part, despite their decreased sense of ownership of their own affected limb reported in other studies [36,37]. In Reinersmann et al.'s [41] study, the strength of the illusion was not significantly related to the subjective distortion of

body representation as measured by the "neglect-like" symptoms questionnaire [35], which also includes questions about perceived ownership of the painful limb (although see their analysis of a subgroup of right-CRPS participants who reported more distorted perception of their affected limb, and weaker ownership of a rubber hand, than left-CRPS participants [41]). This is consistent with the findings that the perceived ownership of a rubber hand does not necessitate a disownership of one's real hand [99]. Because these two phenomena appear to be independent, people with CRPS could have normal susceptibility to rubber hand illusion [41], and still experience a decreased sense of ownership of their own affected limb, as reported in other studies [36,37].

The second conclusion that can be drawn from Reinersmann et al.'s [41] study is that people with CRPS have an intact ability to integrate visual and tactile information (because they have normal susceptibility to the rubber hand illusion). Consistent with this finding, the aforementioned tool use study by Vittersø et al. [51], showing more pronounced updating of bodily representations, also demonstrated intact visuo-tactile integration in participants with CRPS. These two studies suggest that the multisensory mechanisms that contribute to body representation are intact. Thus, a deficit in multisensory integration per se does not seem to be a plausible explanation for distorted body representation in CRPS. Alternatively, a specific impairment in integration of *proprioceptive* information with other sensory inputs could drive these distortions. People can experience subjective ownership of a rubber hand without feeling a proprioceptive drift of their real hand towards the artificial limb [100]. Although the proprioceptive effect of the rubber hand illusion was not measured in Reinersmann et al.'s [41] study, this sensory modality has been investigated in the context of an artificial finger illusion discussed below.

Reinersmann et al.'s [41] study suggests intact visuo-tactile integration in people with CRPS by virtue of a normal rubber hand illusion. On the other hand, a study by Wang et al. [64] suggests that despite impaired proprioception, they can integrate tactile and proprioceptive information and normally experience a multisensory illusion. In their study, people with CRPS were less susceptible to an artificial finger illusion, compared to healthy controls, when only proprioceptive information was available [64]. In the illusion, the hands are positioned one above the other, aligned vertically but some distance apart, and obscured from the participant's view. The index finger of the bottom hand is placed snugly in a pipe, and the index finger of the top hand is placed adjacent to (proprioceptive only condition) or grasping (proprioceptive and tactile condition) an artificial finger. Typically, both of these conditions create an illusion that the hands are closer together in vertical distance than they are in reality [64]. Regardless of which hand (affected or unaffected) was positioned on the top or bottom, this effect was not found in people with CRPS when they were not grasping the artificial finger. Interestingly, people with CRPS did experience the illusion to a similar extent as healthy controls when they received tactile input (i.e. while grasping the artificial finger). This study suggests that although proprioception itself might be

altered in CRPS, it can still be integrated with any available tactile information and result in normal performance on a multisensory bodily illusion [64]. The findings of Wang et al. [64] complement those of Reinersmann et al. [41] from the rubber hand illusion with explicit involvement of proprioceptive information, and further support the conclusion that people with CRPS have intact multisensory integration.

3.1.5. Summary of changes in body representation

Across the current literature, people with CRPS consistently report symptoms pertaining to altered body representation include asomatognosia, distorted perception of the affected parts of the body, and negative feelings about the affected limb. These findings arise not only from self-report measures, but are in agreement with experimental tests of body representation such as limb laterality recognition [56–60], as well as limb size matching and limb position matching [44,49,50,52–54]. However, manual estimates of body midline were not consistently impaired in people with CRPS [38,55]. Body representation relies on the dynamic integration of visual, tactile, and proprioceptive information. Broadly speaking, multisensory integration seems to be intact in people with CRPS and thus cannot account for their distorted body representations. The availability of visual cues can improve (but not fully normalize) position sense for the affected limb [52], suggesting that visuo-proprioceptive integration is possible. The effects of tool use, the rubber hand illusion, and the artificial finger illusion suggest intact visuo-tactile [41,51] and tactile-proprioceptive [64] integration. When whole body movement is concerned [48], auditory-proprioceptive integration can modify subjective perception of the body. Thus it appears that people with CRPS are able to experience certain body-related multisensory illusions [41,48,64] and their performance on proprioceptive tasks improves when congruent input from additional senses is available [52]. Furthermore, people with CRPS are able to update the representation of their body [48], but this process might differ between the affected and non-affected side [51]. Greater updating of bodily representations in people with CRPS compared to pain-free individuals suggests that these representations might be less stable in CRPS [51].

Deficits in systematically measured aspects of body representation mostly appear to arise when people with CRPS have to rely on proprioception, and additional sensory cues are either missing (e.g. when positioning the affected limb with eyes closed [52]) or are incongruent with other senses or motor commands (e.g. when visual feedback about the movement is altered [44]). One possible explanation is that proprioceptive information from the affected limb is not reliable. Sometimes proprioception is impaired in the analogous unaffected limb, too [44,52], which potentially occurs through central mechanisms since in this case the core symptoms of CRPS are not present. There is evidence that we integrate different sensory cues by adaptively making a weighted linear average based on the reliability of each sensory modality [101,102]. Therefore disrupted reliability of proprioception in people with CRPS could mean that the weighting of other senses (e.g. vision) is stronger to compensate [102,103]. Overall, there is consistent

evidence that multisensory integration in CRPS is intact. This mechanism is known to contribute to building and updating multimodal body representations [79,104], and both are governed by similar parietal networks [104–107]. However, neither multisensory nor unisensory representations were directly linked to self-reported body perception disturbance in CRPS [44,52] (for exceptions, see [41,48]). Because multisensory integration is intact, it cannot explain the distorted body representation in this population. Therefore, other, potentially higher-level mechanisms might contribute to these distortions.

3.2. Lateralised spatial cognition

In addition to the distortions in body representation discussed in the previous section, many people with CRPS report symptoms resembling the hemispatial neglect syndrome ("neglect") that can follow a brain lesion. Neglect is an attentional deficit in sensation, movements and / or representations of the contralesional (usually left) side of body and / or space that cannot be completely attributed to a sensory or motor loss [81]. It most often occurs following lesions to the right inferior parietal lobe and temporo-parietal junction [108–111], but can also stem from lesions to other cortical and subcortical areas, such as the mid superior-temporal gyrus, angular gyrus, basal ganglia, and thalamus [112]. Neglect has served as an analogy to describe some of the neuropsychological symptoms found in CRPS. Thus, it is important to consider which aspects of higher cognition are affected in post-stroke patients to systematically characterise related deficits in chronic pain patients. Table 3 summarises examples of deficits shown by people with neglect following brain lesions in different perceptual, motor, and representational modalities; egocentric and allocentric reference frames; and personal, peripersonal, and extrapersonal regions of space[1] (for a comprehensive review, see [81]).

Although CRPS is generally not associated with any brain lesions, the unilateral nature of CRPS means that we could expect any cognitive deficits to be predominantly associated with the activity of the hemisphere contralateral to the painful side. However, thus far the evidence for such lateralised manifestations of neuropsychological symptoms in CRPS is not straightforward. In the following sections, we review research regarding spatially lateralised cognitive functions in CRPS, with the primary focus on spatial attention. We aim to discern the discrepancies in the direction of lateralised spatial deficits in CRPS, and the particular conditions under which they manifest. Finally, we attempt to integrate the changes in spatial cognition with the evidence of distorted body representation.

[1] In addition to our use of "reference frames" when distinguishing between egocentric and allocentric encoding of space, "reference frames" can also be used to refer to the distinction between the ways that information in personal, peripersonal, and extrapersonal space is encoded and represented. However, to enable a clear discussion of the overlapping and distinct spatial effects in egocentric / allocentric representations versus personal / peripersonal / extrapersonal representations, in this paper we reserve the term "reference frames" for the former distinction and "regions of space" for the latter distinction.

Table 3 *Post-stroke hemispatial neglect symptoms*

Domains	Categories	Deficits
Modality	Perceptual neglect	Difficulty with allocating attention to visual, tactile, or auditory stimuli appearing on the contralesional side of space
	Motor neglect	Reduced or slowed movements using the contralesional limb that cannot be attributed to primary motor deficit; reduced or slowed movements in / towards the contralesional side of space
	Representational neglect	Problems imagining or visualising the contralesional side of scenes
Reference frame	Egocentric	Underrepresentation of contralesional side of space in relation to one's own body / body parts (e.g. subjective estimate of one's body midline or straight-ahead shifted towards the ipsilesional side)
	Allocentric	Underrepresentation of contralesional side of spatial relationships between external objects separated in space (e.g. bisections of straight line shifted toward the end corresponding to the ipsilesional side)
Region of space	Personal	Reduced attention to contralesional side of the body
	Peripersonal	Reduced attention to contralesional side of the space within one's reach
	Extrapersonal	Reduced attention to contralesional side of the space beyond one's reach

3.2.1. Self-report and clinically assessed "neglect-like" symptoms

The first published evidence for systematic spatial biases in CRPS come from clinical reports [33] and self-administered surveys [36] reporting motor and cognitive changes consistent with neglect of the affected limb. Galer et al. [33] observed "motor neglect" in CRPS, specifically slower movement initiation (hypokinesia), slower movement execution (bradykinesia), decreased movement amplitude (hypometria), and decreased spatial extent of movements performed with the CRPS-affected hand compared to the unaffected one. Further signs of motor neglect in CRPS are patients' reported need for directed attention to move the affected limb, and the occurrence of involuntary movements. There are also anecdotal reports of patients who failed to move the CRPS-affected limbs when they were concealed from view despite being convinced that they were performing bilateral arm movements [113]. This phenomenon might be characterised as motor extinction (a deficit of motor production that either worsens or only becomes apparent during bilateral movements [114]), although the authors did not report if performance with the affected limb was better when making unilateral movements under the same conditions. "Cognitive neglect" as defined by Galer and Jensen [36] involves feelings of foreignness and lack of ownership over the affected limb. However, the authors never intended for the term "neglect" to be taken literally in the context of CRPS, and we argue that these symptoms more closely resemble body representation distortion than hemispatial neglect (see section 3.1.1.). Between 17% and 90% of patients with CRPS report motor and / or cognitive "neglect-like" symptoms as defined above [33,35–40,42,62]. Also, the frequency [39] and severity of these self-reported

symptoms appears to be greater in CRPS than other pain conditions [35]. Thus, based on this clinical and self-report evidence, it could be argued that people with CRPS present with neuropsychological deficits that resemble hemispatial neglect and related syndromes of body awareness, such as asomatognosia (loss of ownership) [82] and misoplegia (dislike or hatred of the affected limb) [84].

3.2.2. Standard neuropsychological tests of neglect

Following the self-reports of neuropsychological symptoms resembling neglect, some researchers pursued a more objective assessment of these deficits in CRPS by administering classic neurological assessments and pen-and-paper tests that are typically used with brain-injured patients. During confrontation testing, a standard neurological assessment of neglect, patients with post-stroke hemispatial neglect typically fail to report seeing or feeling targets presented on the contralesional side, indicating extinction (when the failure is only during bilateral stimulation) or neglect (when the failure is also during unilateral stimulation). Confrontation testing performed by Cohen et al. [71] revealed that only three out of the 22 tested people with CRPS presented with tactile extinction, while Förderreuther et al. [37] did not observe either neglect or extinction in individuals with CRPS. Five of Cohen et al.'s [71] participants, however, showed tactile allochiria (i.e. perceiving unilateral touch only in the analogous contralateral location), which has been reported in several modalities in hemispatial neglect patients [115–118].

One of the classic bedside tests of hemispatial neglect involves dividing a straight horizontal line in half [119]. For example, a patient who has reduced attention to the left side, relative to the right, would ignore the left end of the line and place the bisection mark further to its right side. A deviation from the centre is thus indicative of spatial attention bias. In CRPS, there are only single case studies reporting deviations in classic line bisection performance: one *away* from the affected (right) side of space [65] and one *towards* the affected (left) side of space [53,54]. Interestingly, Christophe et al. [53] describe that the patient in their study showed a bias towards the affected side when line bisection was performed with either the healthy or affected hand and the line was positioned at body midline. However, the bias was abolished when was positioning the to-be-bisected line in the affected side of space abolished the bias. These single case reports point towards impaired perception of spatial relationships between external objects (allocentric frame of reference) located within reaching distance (i.e. in peripersonal space) [81]. Although the direction of the bias relative to the affected side is inconsistent between the two cases [53,54,65], both patients presented with a leftward bias. This appears to be consistent with a third type of abnormal bisection performance that has been reported for people with CRPS, which was found in robot-assisted line bisections performed with the healthy limb [66]. In this group study, independent of the CRPS-affected side of the body, participants' bisections consistently deviated towards the left relative to those of the pain-free controls. These findings resemble an exaggeration of "pseudoneglect". That is, healthy controls show the consistent leftward deviation

of bisection judgements on some spatial tasks, which is interpreted as an effect of right-hemisphere dominance in spatial perception [120–122]. Finally, several group studies of people with CRPS have reported no signs of line bisection bias relative to healthy controls [37,38,40,55,58] when the task was performed with either the affected or unaffected hand. No lateralised impairment was found on other classic bedside tests of neglect, for example, clock-drawing, clock-reading, rod orientation, Kohs blocks, or block tapping [38].

Overall, the performance of people with CRPS on confrontation testing and standard neuropsychological tests does not provide sufficient support for the hypothesis that CRPS involves neglect of the affected limb or side of space. Some findings even suggest the opposite direction of spatial bias or exaggerated "pseudoneglect". The inconsistence between the normal performance of people with CRPS on classic bedside tests of neglect in most studies, despite the high percentage of self-reported "neglect-like" symptoms in large sample studies (e.g. [35,36,39,42]), might stem from the differences between what these two types of measures entail. That is, the questionnaire about "neglect-like" symptoms measures asomatognosia and motor aspect of neglect, whereas classic bedside tests of neglect primarily measure its perceptual aspect (although they usually require motor responses, too). Another possibility is that classic neglect tests are not sufficiently sensitive to reveal the subtle neuropsychological changes in CRPS, given that classic pen-and-paper tests of neglect were developed to test people who suffered brain lesions, and neuropsychological changes in CRPS are likely to develop because of less overt structural and / or functional changes.

3.2.3. Sensitive measures of lateralised cognitive functions

Inconsistent findings regarding the spatial bias in people with CRPS led some researchers to measure lateralised spatial cognition using methods that are more sensitive. Substantial research on lateralised spatial deficits in brain-lesioned patients and healthy controls has revealed that better precision and sensitivity of assessment can be achieved through experimental manipulation of the properties of the stimuli used to measure attention, spatial representations, and motor control; and by altering the conditions under which these tasks are performed. Below we present the evidence available from several sensitive measures of lateralised changes: the subjective body midline task, temporal order judgements, mental number line bisection, and tests of spatially defined motor control. Through these tasks, researchers have found evidence for biases in people with CRPS on the following domains of spatial cognition: the egocentric frame of reference, tactile spatial attention in personal space, visual spatial attention in personal and peripersonal space, the internal representation of space, and spatially defined motor control.

3.2.3.1. Subjective body midline

In the visual subjective body midline judgement task (or "visual straight-ahead"), participants verbally indicate when a light moving horizontally from one side of extrapersonal space to the

other crosses the point that is directly in front of the middle of their body. When performed in the dark, with no other visual cues available, the task is thought to measure any lateral shift of the egocentric frame of reference, defined as the coding of the location of external objects in relation to one's own body midline [68,123,124]. Multiple studies reported a deviation of subjective body midline towards the affected side of space in people with CRPS compared to healthy and pain controls when judged in a darkened room (median deviation from objective midline ranging from 0.59° to 5.13° [53,54,67–69]). The people with CRPS showed no bias in body midline under illuminated conditions when it is possible to make use of the allocentric frame of reference (external cues). This suggests that if people with CRPS have a distorted subjective body midline, it affects only the representation of external space in relation to their own body. Christophe et al. [53] also demonstrated a distance-based dissociation in one patient who showed a significant deviation towards the affected side when stimuli were presented at two meters distance from the trunk (similar to other studies cited in this section), but not at one meter. The spatial bias of egocentric frame of reference towards the affected side is consistent with an over-representation of the affected relative to unaffected side of space. In contrast to the above findings, Reinersmann et al. [40] found that their participants with CRPS made subjective body midline judgements that were biased further towards the left than healthy and pain controls (0.7° vs. 0.1° and 0.09°), irrespective of which side of the body was affected. This pattern can be interpreted as exaggerated "pseudoneglect", consistent with the previously discussed findings from the robotic line bisection study by Verfaille et al. [66], and could be due to disruption of right-hemisphere cortical networks involved in spatial processing. Visual straight-ahead biases, both towards the affected side and towards the left side, suggest that people with CRPS can have problems with combining external visual information with their subjective body midline. Yet other authors demonstrated that people with CRPS showed no bias when judging their body midline using the visual straight-ahead task [42,55]. Thus, it appears that any shifts of egocentric frame of reference are subject to high individual variability because these effects do not always replicate.

3.2.3.2. Temporal order judgement

According to the law of prior entry, attended stimuli are perceived before unattended ones [125,126]. This principle forms the basis of Temporal Order Judgement (TOJ) tasks. In TOJ procedures, the participant is presented with pairs of identical stimuli, one on each side of space, with different onsets. They report the temporal order of the two stimuli, that is, which occurred first / second. The pattern of left-right responses across different stimulus onsets indicates whether participant's attention is shifted towards one side of space relative to the other. The TOJ task is a sensitive measure of lateralised spatial attention, that is, the distribution of covert attention in one side of space relative to the other.

On tactile TOJ tasks, people with CRPS exhibited reduced attention to tactile stimulation applied to the affected limb (i.e., touch on the affected limb had to occur ~17-27ms before touch on the

unaffected limb for the two stimuli to be perceived as simultaneous [58,72,73]; however, Filbrich et al. [74] failed to replicate this effect). When the limbs were crossed, their performance indicated inattention to the unaffected hand, now located in the affected side of space (touch had to occur ~18ms earlier than on the affected hand in the unaffected side of space [73]). CRPS participants exhibited the same pattern of attention bias both with and without visual feedback about the limbs' position [72]. Tactile stimulation inherently involves body-relevant information, thus it would seem that the tactile TOJs should rely on a personal frame of reference. However, it appears that those judgements at the same time rely on the current location of the body parts in peripersonal space.

The tactile attention bias away from the affected side also extends to TOJs about visual stimuli presented near [74] or on the surface of the patients' hands and on a blank board in near space [45] (with magnitude of ~14-25ms). In accord with Moseley et al. [73], the authors concluded that visual attention bias in CRPS is space-based, because it was observed regardless of the involvement of the body. However, Bultitude et al. [45] also found no lateral shift of visual attention when the limbs were crossed such that the affected limb was located in the unaffected side of space. This suggests that people with CRPS had a deviation in attention both away from the affected side and from the affected limb (regardless of where it was located), which cancelled each other out when the limbs onto which the visual stimuli were presented were crossed.

Despite evidence for spatial attention bias from TOJs, these deficits do not seem to affect all aspects of visual spatial attention in CRPS. Filippopulos et al. [75] argued that attention deficits in CRPS do not involve allocation of visual attention, as they failed to find any delay of orienting saccades to cued and non-cued visual targets presented in either hemifield. Similarly, no spatial bias away from the affected side of space was found on a computerised task measuring simple reaction times to visual stimuli [38]. The contrasting results on the TOJ tasks and these other computerised tasks might be because of the different regions of space involved, since computer monitors are invariably placed within the participant's extrapersonal space (e.g. at a distance of 60 cm) rather than personal or peripersonal space.

In summary, the results on sensitive tests of spatial cognition in people with CRPS tend to indicate that judgements of their subjective body midline are biased *towards* the affected side, that is, in the direction opposite to what would be expected based on their self-reported "neglect" of the affected limb. Yet, TOJs of tactile and visual stimuli tend to be systematically biased *away* from the affected side of space, and problems with attention allocation [67] cannot explain this bias. Given that both visual and tactile TOJs were affected [45,58,72,73], attention biases in CRPS might be supramodal. On the other hand, when the same individuals were tested on TOJs in multiple modalities, one study found they only presented with visual, but not tactile biases [74]; and another study found they only presented with tactile, but not auditory biases [58]. Similar dissociations between sensory modalities can also be found in neglect after brain injury [127].

3.2.3.3. Mental number line bisection

Analogous to the conventional line bisection task that involves the allocentric frame of reference, the mental number line bisection task is thought to involve the "bisection" of the internal representation of space. It is considered to be an implicit measure of mental spatial representations [128], and is independent of motor abilities. In mental number line bisection, participants verbally indicate, without calculating, the number that is halfway between a given pair of numbers. Because the number line is internally represented from left to right [129–131], a bias towards the higher numbers would be equivalent to a rightward spatial bias, as has been demonstrated in hemispatial neglect [128,132–134]. Midpoint number judgements in CRPS were found to deviate away from the affected side compared to healthy controls [67]. The opposite direction of such a bias was observed in a single case of CRPS of the left limb [53,54], who also presented with a consistent leftward bias on a range of other spatial tasks. Despite this exception, the group study suggests that inattention to the affected side of personal and peripersonal space exhibited by people with CRPS also affects the internal representation of space. In contrast to personal and peripersonal space, mental number line bisection does not rely on bodily information about the affected limb and its position in external space, or the visual representation of the affected side of space. Therefore, biased mental number bisection suggests a generalized distortion of spatial representations in CRPS, which could potentially occur via shared higher-order mechanisms.

3.2.3.4. Spatially defined motor control

Following the early clinical and self-reports of motor "neglect-like" symptoms [33,36], several studies also tested for spatially lateralised deficits in movements using sensitive experimental measures. Contrary to the motor neglect hypothesis, people with CRPS did not show any signs of neglect or extinction on behavioural motor tasks such as finger tapping when performed with one or both hands; in normal posture or with the hands crossed such that the affected limb was located in the unaffected side of space, and vice versa; or with or without visual feedback [53,55]. Similarly, there was no asymmetry (i.e. extinction) in hand movement patterns while performing a bimanual circle drawing task measuring motor accuracy [55]. The performance of people with CRPS on both the tapping and circle drawing tasks did not differ from healthy controls. Another study with a larger sample size (13 vs 7) and a slightly different measure of finger tapping found worse motor accuracy and coordination on circle drawing and button pressing tasks when using the affected limb compared to the unaffected limb, regardless of the side of space in which patients performed the tasks. Importantly, the people with CRPS also showed similar deficits when the tasks were performed on the affected compared to unaffected side of space with the unaffected hand [76]. Thus, there appear to be spatially defined motor deficits in CRPS (that is, deficits modulated by where the movements are performed relative to body midline). It is not possible to ascertain whether the asymmetries between the affected and unaffected limbs and sides of space reported in people with CRPS were greater than normal, because there was no control sample [76]. Nonetheless, the findings of this study are consistent with self-reported "neglect-like"

symptoms, which primarily entail movement difficulties [33,36]. However, another perspective that we will now outline is that motor deficits in CRPS arise from decreased use of the affected limb rather than attention bias [3].

Punt et al. [3] proposed a learning-based account for motor deficits in CRPS framed as non-use of the affected limb. Learned non-use manifests as motor difficulties greater than expected based on actual physical constraints, or as a difference between what the patients do spontaneously and what they are able to do in clinical examination. This could explain why motor "neglect-like" symptoms are reported by the people with CRPS, but not necessarily apparent upon experimental testing [55]. After a stroke, learned non-use develops through operant conditioning and can affect the entire contralesional side of the body. Punt et al. [3] argued that in CRPS learned non-use is normally limb-specific rather than involving the entirety of one hemibody and could manifest in protective behaviours (e.g. guarding and holding an affected hand close to the chest). However, despite these differences in the manifestation of learned non-use in CRPS compared to stroke, its progression is thought to follow a similar pathway [3]. Limb trauma is followed by enforced immobility, leading to poor coordination and dexterity, which result in less frequent attempts to move. Movement is additionally suppressed by pain and fear avoidance behaviours [135]. At the same time, compensatory movements of the unaffected limb are developed and reinforced. These changes can alter cognitive and cortical representation of the CRPS-affected limb [3]. For instance, primary somatosensory and motor cortical representations of the affected hand were found to be smaller (compared to the unaffected hand and to representations of healthy controls) [85,86,136–141], consistent with underutilization, while the sensory map of the unaffected hand was found to be enlarged [142], consistent with compensatory use (although these findings have recently been disputed [143]).

In contrast to the framework of motor neglect that attributes spatially-defined motor impairments to attentional deficits, the proposal of Punt et al. [3] explains motor control deficits using a learning-based theoretical account. In an attempt to dissociate these two possible explanations of visuo-motor deficits in CRPS, Verfaille et al. [66] analysed goal-directed movements of the unaffected limb to bisect horizontal lines in both sides of space. Contrary to the neglect framework, the bisections of participants with CRPS did not show a bias in relation to the affected side, nor depending on in which side of space the bisections occurred. Nonetheless, they showed a significant leftward bias, consistent with exaggerated "pseudoneglect". This finding opposes the learned non-use account, because the participants performed the bisections with the unaffected limbs. To disentangle the account of motor neglect, future research could investigate if there are any signs of directional hypokinesia or bradykinesia in CRPS. If people with CRPS show performance asymmetries analogous to that of patients with hemispatial neglect after brain injury, they should have slower initiation or execution of movements directed towards the affected side of space compared to movements directed towards the unaffected side of space, even when the

unaffected hand is used. All movements in Verfaille et al.'s [66] study were directed towards the CRPS-affected side of space, and thus it was not possible for their study to discern directional "neglect-like" motor changes. Nonetheless, even based on the evidence available thus far, attention-based and learning-based explanations are not mutually exclusive, and some changes in motor control in CRPS could arise from a combination of both.

Although Punt et al. [3] sought to separate perceptual and motor aspects of neglect, we propose that their learned non-use hypothesis can also provide a basis for explaining how perceptual spatial biases could arise in CRPS. Previous studies involving amputees and healthy participants with limb immobilization provide evidence in favour of action-driven spatial representations (see also [144]). Specifically, upper limb amputees were found to "neglect" the side of near (but not far) space corresponding to their missing arm [145], and in healthy participants experimental cast immobilization of one arm led to shrinkage of its peripersonal space [146]. These findings suggest that lack of limb action can change the representation of space surrounding that limb. Because of decreased mobility of the affected limb, people with CRPS perform fewer movements in the affected side of near space. We hypothesise that this could give rise to changes in the cognitive representation of space. Underrepresentation of the CRPS-affected side of space could potentially hinder the ability to perform motor tasks on that side, in line with spatially-defined deficits in motor accuracy and coordination found in people with CRPS [76]. It could also contribute to reduced attention to that side of space demonstrated in TOJ studies [45,58,72–74].

3.2.4. Summary of changes in lateralised spatial cognition and potential mechanisms

Overall, research suggests people with CRPS might present with neuropsychological deficits resembling hemispatial neglect that can follow a stroke. However, the evidence is not consistent. Researchers have rarely found lateralised spatial biases using standard bedside measures of neglect, or using sensitive measures such as saccades and reaction times to visual targets, auditory TOJs, and some experimental measures of motor performance. Other sensitive tests of perceptual (visual or tactile TOJs) and representational (mental representation of space) changes have revealed lateralised deficits in spatial cognition consistent with a bias *away from* the CRPS-affected side of the body and / or space. Yet other findings from visual subjective midline judgements point to a shift of egocentric frame of reference *toward* the affected side in CRPS, thus in the direction opposite to what would be expected for neglect of the affected side. The opposing biases *away from* the affected side of space in TOJ tasks and *towards* the affected side in visual subjective body midline cannot be explained by the different modalities that are tested in these tasks, because TOJs were biased in the visual domain. We consider two possible explanations for these opposing biases: the dissociation between near and far regions of space, and the distinct functional aspects of peripersonal space (defensive and goal-directed).

3.2.4.1. Near space versus far space

The different regions of space in which participants perform the TOJs and subjective body midline judgements could potentially account for the inconsistent biases shown by people with CRPS on these tasks. The studies using visual subjective body midline judgements in CRPS presented stimuli in far / extrapersonal space (generally two meters away from the trunk). The studies using TOJs, on the other hand, presented stimuli in either personal space (e.g. tactile TOJ, visual TOJ when stimuli are presented on body surface) or near / peripersonal space (e.g. visual TOJ when stimuli are presented on a blank board within arms' reach, or immediately next to the hands). Like perceptual TOJs, the internal representation of space (as measured through mental number line bisections) is also biased away from the affected side. Dissociations between distinct regions of space have been found in some post-stroke hemispatial neglect patients, where attention deficits manifested either exclusively in their personal space [147], near / peripersonal space [148], far / extrapersonal space [149,150], or internal representation of space [132,151]. Although rare, there are reports of individual patients with post-stroke neglect [152–155] who show opposite directions of bias on different tasks, as also reported in Sumitani et al.'s [67] CRPS study (opposing biases in subjective body midline and mental number line bisection).

3.2.4.2. Defensive versus goal-directed space

Above we have suggested a possible explanation for the inconsistent biases shown by people with CRPS on TOJ and visual straight-ahead tasks based on known cortical dissociations between the representation of near and far space identified through research on brain-lesioned patients. However, given that people with CRPS typically do not have any history of brain damage, it could be more meaningful to consider potential cognitive mechanisms that might better account for the different results on this task. Peripersonal space is thought to dissociate into two representations according to distinct functions: for preparing defensive responses (defensive peripersonal space), and for preparing actions (goal-directed peripersonal space) [156]. Furthermore, Bufacchi and Iannetti [157] argue that peripersonal space cannot be defined in terms of fixed boundaries around the body (or body part), but its extent is rather graded and dynamically changing according to the action being performed and the proximity or valence of external information. Thus, we speculate that different dynamic changes to goal-directed and defensive peripersonal space specific to the affected extremity [158] might explain the contrasting biases that have been reported in people with CRPS at different distances from the body. Reduced activity of the affected limb [3], resulting in fewer interactions with the affected side of goal-directed peripersonal space, could reduce visuospatial processing near the body in the affected compared to unaffected side. For example, Makin et al. [145] found that visuospatial processing of amputees favoured their intact side when stimuli were presented at a distance of 50cm. The biased TOJs in people with CRPS were observed within the same distance (see also [158] for a review of how peripersonal space is shaped by action and integration of multisensory information from the body and the environment). In contrast, it has been shown in healthy participants that approaching, threatening stimuli can

extend peripersonal space in such a way that is sensitive to the trajectory of the threat [159,160]. No studies have measured the dimensions of the affected side of defensive peripersonal space in CRPS. However, we suggest that it could be enlarged due to heightened hypervigilance to threat, as has been reported for the representation corresponding to the affected area in trigeminal neuralgia [161]. This could explain why people with CRPS showed greater tool-use dependent updating of peripersonal space than controls [51], which could indicate that their spatial representations are less stable. It is conceivable that such a heighted defensive awareness to stimuli that are potentially threatening to the CRPS-affected limb (due to allodynia and hyperalgesia) could drive a bias towards the affected side in extrapersonal space. This might particularly be the case for dynamically moving stimuli such as those used in the visual subjective midline task. This speculation should, however, consider that the visual subjective body midline in CRPS has typically been assessed at two meter distance from the trunk, which is beyond the extent of peripersonal space normally reported in healthy participants (80-90cm [162]). Body midline judgements made at one meter were not biased in a case of CRPS [53], similar to a group study that reported no bias on visual TOJs for stimuli presented 90 cm from the trunk [74]. However, thus far, no studies have mapped the extent of defensive peripersonal space in people with CPRS in the context of threatening and / or dynamically approaching stimuli (note that the TOJ stimuli appeared in a fixed distance from the participant's body). Spatial representations can be dynamically changing depending on the conditions and the meaning of the testing stimuli. Therefore, an enlarged defensive yet diminished goal-directed peripersonal space representation of the affected side could still account for the seemingly contradictory findings of attention bias in CRPS.

On balance, the discussed findings suggest that CRPS is associated with contrasting alterations in spatial attention, representations of space, and spatially defined motor control. The neuropsychological changes in these domains are observed in different modalities (visual and tactile), and different regions of space (personal, peripersonal, extrapersonal, and representational). The existing evidence cannot fully account for the conflicting directions of the spatial biases that have been reported (towards or away from the CRPS-affected side). Yet hypothetically, some of the contrasting patterns of performance in the spatial tasks could be explained by hypervigilance to approaching stimuli within the affected side of extrapersonal or defensive peripersonal space, simultaneous to "neglect" of the affected side of personal and goal-directed peripersonal space stemming from learned non-use.

3.2.5. Overlap of body perception distortion and "neglect-like" symptoms

Thus far, we separately reviewed evidence for body perception disturbances and deficits in lateralised spatial cognition in CRPS. However, these two cognitive functions are inherently linked (e.g. spatial representations are anchored in the represented location of the body [158,163]), and neuropsychological changes in them often present simultaneously [45,58]. Somatosensory,

motor, and body representation distortions are largely confined to the CRPS-affected limb (although bilateral and hemisensory deficits have also been reported, e.g. [23,26,52,164]), thus they can be considered primarily lateralised. This is comparable to the changes in spatial cognition discussed so far, which most often take the CRPS-affected side as a point of reference. Whether problems with body representation and attentional orienting are truly dissociable in CRPS remains uncertain. For instance, Reid et al. [58] suggested that interactions between spatial attention and processing of body-relevant information (e.g. seeing the limbs) might exacerbate usually subtle lateralised spatial changes by evoking distorted body representation.

3.2.5.1. The "Somatospatial inattention" hypothesis

Some spatial biases might only manifest when the body is directly involved in the task at hand, demonstrating an overlap of the cognitive changes in body representation and spatial attention. When directly investigating these interactions, Reid et al. [58] found a deviation away from the affected side in people with CRPS when line bisections were performed on the surface of their hands, but not when performed on paper. This perceptual bias was space-dependent because it was present not only on the affected limb, but also on the healthy limb when placed in the affected side of space. Participants with CRPS exhibited a similar deviation away from the affected side when they bisected the length of their affected hand and forearm [58]. Interaction between spatial bias and body representation was also demonstrated by difficulties with recognising the laterality of body parts specifically when they were presented in the affected hemifield [58]. Based on this evidence, and the previously found attention bias away from the affected side on tactile TOJs, Reid et al. [58] proposed that the disruption of spatial processing in CRPS specifically involves problems with integrating spatial information with body representation, a phenomenon they called "somatospatial inattention". This hypothesis was partially supported by Filbrich et al. [74], who found a significant attention bias in visual TOJs only when patients' hands were positioned close to the visual stimuli in near space, but not when the hands were out of sight, close to the trunk. Deviated visual subjective body midline in CRPS [67–70] is also somewhat in agreement with this hypothesis since this measure requires integrating body midline with the external visuospatial reference frame. However, in this case the performance of people with CRPS is consistent with over-representation of the affected side rather than inattention. Furthermore, the proposed "somatospatial inattention" does not fully account for all spatial attention biases found in CRPS, because significant deviation away from the affected side was also observed in visual TOJs for stimuli that did not involve and were not near to any body parts [45].

3.2.5.2. Proposed mechanisms of interactions between bodily and spatial representations

We suggest there are two hypothetical mechanisms through which body representation disturbances might drive attentional biases even when body parts are not directly involved in the spatial tasks: reduced ownership and increased perceived size of the CRPS-affected limb. More generally, body representation forms the basis for spatial cognition [158,165]. In CRPS, reduced

awareness and ownership of the painful limb could contribute to inattention to the affected side. For example, the severity of body perception disturbance was found to predict the magnitude of spatial attention bias away from the affected side in people with CRPS [45]. Furthermore, a perceived increased size of the affected extremity [49] could conversely drive hyperattention to that side.

Peripheral CRPS symptoms in the affected limb might offer an additional explanation of how body-related disturbances could drive attentional biases. First, it has been suggested that the bias in visual subjective body midline judgements towards the CRPS-affected side is due to an exaggerated somatosensory input from the painful limb [68,166]. Second, CRPS signs can manifest as a combination of sensory gain (e.g. pain, hyperalgesia) and sensory loss (e.g. hypoesthesia) [167]. Thus, suppression of some types of somatosensory input could potentially explain tactile inattention to the affected limb (e.g. on TOJ tasks when the hands are uncrossed). Third, mechanical constraints related to motor symptoms of CRPS can trigger underutilization of the affected limb [3]. As we argued in in section 3.2.3.4., such underutilization could lead to space-based inattention, because fewer movements performed in the affected side of space would drive asymmetries in spatial representations. Although these peripheral somatosensory and motor abnormalities are not equivalent to distorted body representation, this representation is generated and continuously updated based on multimodal sensory input and motor feedback during action [79,80,158,165]. Therefore, the peripheral (somatosensory and motor) and central (body representation) mechanisms could serve as complementary explanations of how body-related information could exacerbate spatial biases, even when that information is not directly relevant to the task. Nonetheless, direct empirical evidence for how body representation, somatosensory, and motor disturbances might shape spatial processing in CRPS is limited and it remains unclear why the attention bias is sometimes found to be shifted away and sometimes towards the CRPS-affected side.

In conclusion, people with CRPS show several changes to lateralised spatial cognition. These share many similarities with hemispatial neglect, yet there are also several differences. Although the abovementioned aspects of body representation disturbance might relate to lateralised attention deficits, they should not be treated synonymously (i.e. as “neglect-like” symptoms). A distinction between the two concepts can help to avoid theoretical, terminological, and mechanistic confusion in research.

3.3. Non-spatially-lateralised cognition

In addition to changes in body representation and lateralised spatial cognition reviewed thus far, people with CRPS can also present with cognitive deficits that are not lateralised with respect to the affected side of the body or space. In this section, we discuss non-lateralised cognitive processes that comprise aspects of both spatial and non-spatial cognition. Examples of potentially

affected aspects of non-spatially-lateralised spatial cognition include spatial orientation; memory for spatial locations; visuospatial exploration and coordination; constructional abilities; and knowledge about the orientation and order of objects, letters, or numbers. Examples of potentially affected aspects of non-spatially-lateralised non-spatial cognition include numerical and language processing, recognition of objects and faces, imitating complex movements, generalised attention, working memory, and executive function. Broadly speaking, these can be broken into cognitive functions that have been associated with the parietal lobe; and executive functions, memory, and language.

3.3.1. Parietal functions

Comprehensive standard neuropsychological assessments of people with CRPS revealed no systematic abnormalities in spatial orientation, visual exploration, constructional abilities, spatial memory, or visuospatial coordination on a group level, compared to healthy and pain controls [38]. However, Cohen et al. [71] assembled a custom battery of standard neuropsychological tests to assess functions specifically associated with the parietal lobe. They found that 68% of their tested participants with CRPS showed one or more deficit in the ability to: recognise objects by touch (astereognosia), identify the fingers of the hand (finger agnosia; see also [37,77]), identify numbers outlined on the surface of the hand (dysgraphaesthesia), draw objects (constructional apraxia), comprehend arithmetic (dyscalculia), write (dysgraphia), repeat speech (conductional dysphasia), differentiate between the left and the right side of the body, and / or imitate gestures or tool use (ideomotor apraxia). Deficits like these all typically occur after parietal lobe lesions [168]. However, the assessed individuals with CRPS had never sustained brain injury that could account for these deficits (confirmed by normal MRI scans in 12 out of 22 patients), and had not had any cognitive difficulties prior to the onset of CRPS symptoms (corroborated by their families). None of the healthy control participants tested on a shortened version of the same battery presented with any neuropsychological deficits, suggesting that these symptoms could be due to CRPS-related functional cortical reorganization of the parietal networks. Although tested on both upper limbs, the abnormalities on the manual and tactile / haptic tests were only present on the affected side of the body of participants with CRPS. This means that some of the observed deficits could be attributed to peripheral sensory loss or motor impairment. However, 27% of patients with lower-limb CRPS also presented with behavioural deficits despite being tested on their unaffected upper limbs [71]. Therefore, it is likely that at least some of the reported changes are due to cortical reorganization that driven by parietal changes.

There are also reports from this and other studies of individual people with CRPS who presented with more unusual and severe non-spatially-lateralised deficits. Cohen et al. [71] reported cases of horizontal inversion of individual letters and words, and inverted ordering of letters or numbers, in spontaneous writing (resembling a form of dysgraphia [169]), although people with CRPS did not show any impairment of letter orientation recognition in a different study [58]. These deficits

were apparent when patients used their affected limb, and, in one patient - bilaterally. Robinson et al. [65] also presented a case of a right upper-limb CRPS patient with no history of brain injury who exhibited mirror reversal in writing single words with his unaffected hand and in reading single letters. Mirror writing is rare but can follow various focal lesions to the left hemisphere [170,171]: the hemisphere contralateral to this patient's CRPS-affected hand. The same patient also presented with severely impaired face perception (i.e. prosopagnosia, a neuropsychological symptom that can occur following a lesion to fusiform gyrus on the ventral surface of the temporal lobe [172]) that had not been present prior to the development of CRPS. Despite being able to visually recognise and name objects, the patient failed to recognise if objects were in the upright orientation and he copied objects into inverted orientations. Orientation agnosia is most commonly found in patients with lesions to the posterior parietal cortex [173–175].

The studies directly assessing parietal lobe function in CRPS thus far have had relatively small sample sizes and usually lack pain or age-matched control groups (although an unspecified control samples was tested on most of the tasks in Cohen et al.'s study [71]). Therefore, it is difficult to estimate the real prevalence of the symptoms discussed above in CRPS. An exception is a study by Kolb et al. [38], who tested for several neuropsychological symptoms linked to parietal function. In this study, people with CRPS on average did not present with any abnormalities that would be consistent with parietal dysfunction. However, the authors did not report individual cases, and for some measures did not specify which hand was tested (for instance, Cohen et al.'s [71] patients were not impaired when using their unaffected hand). We cannot argue that the neuropsychological changes discussed in this section are common in CRPS population, because they were observed only in a proportion of patients or in single cases (see Table 2). Nevertheless, reports of deficits in CRPS that are typical of patients with temporal and parietal lesions suggest a disruption of visuospatial functions that could be due to functional cortical reorganization in these areas.

3.3.2. Executive functions, memory, and language

Although there is evidence for biased *spatial* attention in people with CRPS, not all aspects of attention appear to be affected in this population. Specifically, no differences between people with CRPS, healthy controls, and pain controls were found on measures of alertness (response readiness) and working memory [62]. People with CRPS did, however, have poor temporal acuity when making spatial judgements: in a visual TOJ task they needed larger intervals between the two stimuli to reliably indicate their order of presentation [45]. In another, large sample study (N = 137), 42% of people with CRPS presented with mild dysexecutive syndrome (relative to age- and education-matched normative data), including impaired performance on working memory and verbal fluency tests [78]. Twenty-three percent of people with CRPS showed global cognitive processing impairments. Besides executive deficits, they also demonstrated impaired naming and declarative memory [78]. Executive, naming, and memory deficits are consistent with pathology

of the frontal lobes. Together with the deficits in general (non-lateralised) spatial cognition, problems with language processing also suggest changes to parietal function in CRPS.

3.3.3. Summary of non-spatially-lateralised cognitive changes

In summary, people with CRPS can present with non-spatially-lateralised deficits in higher cognition that resemble impairments found in neurological conditions other than hemispatial neglect. Findings from standard neuropsychological test batteries are still mixed, however, some individuals with CRPS present with neuropsychological symptoms like those shown by patients with lesions to the parietal lobe (e.g. astereognosia, finger agnosia, or constructional apraxia) and / or temporal lobe (e.g. mirror reversal of writing, object orientation agnosia, or prosopagnosia). These unusual symptoms appear to affect only a subset of people with CRPS, yet they demonstrate that changes in visuospatial functions are not limited to lateralised spatial processing biases. Furthermore, people with CRPS can also present with features of dysexecutive syndrome and some language processing difficulties that are typical of frontal and parietal lobe pathology. Hemispatial neglect most often occurs after a lesion to temporo-parietal regions of the right hemisphere [108], which would be expected to disrupt other neuropsychological functions that depend on these networks. Thus, non-spatially-lateralised deficits can also co-occur with neglect. Such changes include impaired sustained attention, impaired selective attention, a tendency to favour local features over global configurations, and deficits in spatial working memory [112] (for reviews, see [176,177]). Yet these symptoms are not diagnostic features of neglect. This combined evidence suggests that the neglect framework is useful but not sufficient for characterising the breadth of neuropsychological changes in CRPS. Instead, disruption of parietal function and / or cortical networks involving the parietal lobe appears to be a better candidate.

Although there is no direct neuroimaging evidence linking parietal cortex to cognitive deficits in CRPS, several studies on sensory and motor function reported altered patterns of activation in parietal regions. For instance, tactile stimulation of the fingers of both hands resulted in weaker superior [77] and inferior parietal lobe [140] evoked responses in people with CRPS compared to healthy controls. Furthermore, relative to healthy people, individuals with CRPS showed greater activation of the inferior parietal lobe during movement (relative to rest) of the affected compared to unaffected hand [178], and when they were observing hand movements (relative static hands) [179]. Finally, another study reported reduced grey matter volume in the inferior parietal lobe in early-stage (less than 10 months) CRPS, compared to healthy controls [30]. These parietal regions have been linked to the perception of space and limb location in other studies [180,181], which supports the conclusion that functional and / or structural reorganization of parietal networks might be associated with neuropsychological symptoms in CRPS. However, further studies are necessary to test this hypothesis and identify the neural underpinnings of these cognitive changes.

4. Clinical relevance of neuropsychological changes in CRPS

In the following sections, we will discuss the clinical significance of aberrant changes in higher cognitive functions in CRPS. Their interactions and relationships with clinical signs of the disorder reflect the role of the neuropsychological changes in the manifestation of CRPS. They can also inform the treatment approaches targeting these higher cognitive changes to improve the clinical outcomes.

4.1. Supraspinal modulation of sensory, motor, and autonomic function

Although this review primarily focuses on higher-level cognition, here we provide examples of cortical modulation of low-level sensory, autonomic, and motor functions in CRPS (Table 4), relevant to understanding the higher-order central mechanisms of clinical signs of this condition. Previous research suggests that resting or seeing the affected limb in the unaffected side of space can normalize the temperature of that limb [72,182] (although this effect is not always found [51]). Furthermore, manipulating the perceived size of CRPS-affected hands can modulate movement-related pain intensity and swelling [183]. Sensory conflicts, such as viewing ambiguous visual stimuli, can increase pain and induce other sensory disturbances, dystonic reactions, and asymmetric autonomic response [184,185]. Sensory disturbances associated with increased pain can also be triggered by sensory-motor conflicts [186]. Heightened susceptibility to such conflicts suggests that CRPS-related sensory impairments might extend beyond the cortical networks related to sensory-motor processing of the affected body parts. Specifically, they can arise from processing visual objects [184,185] or sound [187] unrelated to the body, or during movements of the unaffected arm [186]. People with CRPS also presented with abnormal sensations in the CRPS-affected limb evoked without actual somatosensory stimulation, solely by creating a visual illusion of the affected limb being touched [188]. Overall, the many examples of relief or worsening of symptoms by spatial or multisensory manipulations support the notion that sensory and autonomic abnormalities in CRPS cannot be fully accounted for by peripheral mechanisms and suggest an involvement of supraspinal cortical mechanisms in generating or aggravating physical symptoms of CRPS.

Table 4 *Evidence of modulation of low-level sensory and autonomic functions in CRPS by spatial or multisensory manipulations*

Function	**Manipulation**	**Affected low-level sensory / autonomic / motor function in people with CRPS[a]**	**Study details[b]**
Visual perception	Viewing ambiguous / conflicting visual stimuli	Increased pain (61-73%), sensory disturbances (73%), dystonia (33%) in the affected limb, and asymmetric vasomotor response (34%)	Cohen et al. [184], N=30, HC, BL; Hall et al. [185], N=30, HC, PC
Auditory perception	Hearing uncomfortably loud sound	Painful sensations to sound (hyperacusis; 38%)	de Klaver et al. [187], N=40
Sensory-motor integration	Incongruent mirror visual feedback during active movements	Increased pain and sensory disturbances	Brun et al. [186], N=38, HC, PC, BL
Tactile perception	Mirror visual feedback of stimulated unaffected limb	Pain and paraesthesia experienced in the corresponding location on the non-stimulated affected limb (allochiria); cold perceived concurrently on the stimulated and non-stimulated limb (dysynchiria)	Acerra and Moseley [188], N=10, HC, PC, UL
Temperature modulation	Physically resting or viewing the affected limb as positioned in the unaffected side of space through prism glasses	Normalization of temperature asymmetry between the limbs	Moseley et al. [182], N=10, HC, BL, [72], N=23, HC, BL
Visual perception	Viewing enlarged image of the affected limb through magnifying lenses or in virtual environment, or shrunk images of affected limb through minifying lenses.	Pain and swelling (evoked by movement) increased when viewing enlarged image, reduced when viewing shrunken image	Matamala-Gomez et al. [189], N=9, PC, AL; Moseley et al. [183], N=10, AL

[a]Percentages represent the proportion of individuals with CRPS out of the total CRPS sample who presented with abnormal performance. We reported percentages where available; in other cases, we presented group effects.

[b]N represents CRPS sample size. Where applicable, we specified what control group was included (HC = healthy / pain-free controls; PC = pain controls), and which limb(s) were tested (AL = affected limb; BL = both limbs).

4.2. Neuropsychological symptoms related to pain intensity

Interrelationships between the changes in higher cognitive functions and clinical signs of CRPS further demonstrate the involvement of central mechanisms in the manifestation of the syndrome. For example, higher pain intensity was associated with greater body perception disturbance, longer time taken to recognise the laterality of images of the affected limb, and more impaired sense of limb movement [44,47,57,60]. People with CRPS also reported increased pain intensity

while completing the limb laterality recognition task, which was greater in higher cognitive load conditions (i.e. when limbs were presented for shorter time) [63]. Finally, the severity of spatially-modulated motor deficits [76], self-reported "neglect-like" symptoms [42], and magnitude of spatial attention bias [58,72,73] were related to more intense pain, although several studies reported finding no such relationships [39,40,45,74]. Nevertheless, self-reported "neglect-like" symptoms might have important prognostic value and contribute to the maintenance of CRPS, because they predict pain outcomes six months later in chronic CRPS [42]. The existing behavioural evidence cannot ascertain whether neuropsychological symptoms are primary or secondary to clinical signs of CRPS. However, the reported relationships between these outcomes suggest that cognitive and behavioural interventions targeting changes in processing conflicting information, body representation, and lateralized spatial function, have a potential to improve clinical outcomes in CRPS and other pain conditions.

4.3. Are neuropsychological symptoms specific to CRPS?

One outstanding question is to what extent the neuropsychological symptoms that we have reported here are unique to CRPS. Of those neuropsychological changes we have discussed, space- and body-related neurocognitive phenomena often relate to clinical symptoms of CRPS and might be specific to this pain syndrome. The lateral shift of subjective body midline [40,70], overestimation of the size of the affected limbs [49], referred somatosensation from the healthy to the affected limb under mirror visual feedback [188], and sensory disturbances and increased pain due to viewing conflicting visual stimuli [185] seem to be unique to CRPS. This is because they were not found in control patients with other pain disorders who participated in the same studies.

However, changes in body representation [190], spatial representations [161], auditory perception [191], tactile acuity [192], and proprioception [190] can also be present in other chronic pain conditions. For instance, despite being slower than healthy participants in recognising hand laterality, when the performance of participants with CRPS was directly compared to those with phantom limb pain [62] or other non-CRPS upper limb pain [40], there were no differences compared to these groups. Self-reported "neglect-like" symptoms were also found in other chronic pain conditions, particularly upper limb pain [37,33,36,38,62,40] (although see [35]). Thus, some deficits in body representation and lateralised spatial cognition appear to be present in lateralised chronic pain conditions other that CRPS. Altered body representation was also observed in widespread pain (fibromyalgia) and chronic back pain (for a review, see [190]). People with fibromyalgia also reported similar experiences during sensory-motor conflict as individuals with CRPS [186]. It is thus possible that the above changes in body representation are common features of a group of related chronic pain conditions.

Certain cognitive changes might be associated with chronic pain more generally, regardless of its site and origin. For instance, deficits in working memory, verbal learning and memory, and non-lateralised attention have been found in people with chronic pain other than CRPS [95,193]. A comprehensive literature review by Hart et al. [193] concluded that attentional capacity, processing speed, and psychomotor speed are commonly affected in people with chronic pain (without a history of brain injury) compared to healthy controls. The severity of their cognitive deficits has often been associated with reported pain intensity, and most studies ruled out the effect of medication on the participants' performance. Even when the severity of depressive symptoms is controlled for, approximately 20% of people with non-malignant chronic pain present with cognitive impairment relative to normative cut-offs [95]. Conversely, a meta-analysis revealed no attention bias towards pain-related information in patients with chronic pain other than CRPS [194].

Although an exhaustive review of neuropsychological changes in chronic pain is beyond the scope of the current article, it is clear that many of the neuropsychological changes reported in CRPS are not unique to this condition. Nonetheless, the therapeutic benefit of treating such changes in CRPS suggests that they are important for understanding its pathology. Furthermore, understanding these cognitive symptoms could potentially result in expanding the neurocognitive treatments that are effective in CRPS to other pain populations.

4.4. Targeting neuropsychological changes for treatment of CRPS

The supraspinal mechanisms of CRPS are thought to involve functional cortical reorganization. For instance, the severity of pain and other CRPS signs (mechanical hyperalgesia, tactile discrimination impairment, decreased grip strength, and impaired reach to grasp movements) were related to the extent of functional reorganization of primary sensory and motor cortices [85,86,136,137,139,178,195]. Functional reorganization of the cortical representation of the CRPS-affected limb can be reversed in the course of CRPS treatment [85,196], and such a reversal is associated with improvement of CRPS symptoms. In one study, the patients who initially showed shrinkage of the cortical representation of the affected limb (relative to unaffected limb and representations of healthy controls) [139] were followed-up at least a year later, after successful drug therapy accompanied by physical therapy. Reorganization of the primary somatosensory representations of their CRPS-affected hands was reversed, and this correlated with the extent of the improvement in their CRPS symptoms [196]. Reversal of cortical reorganization of primary and secondary sensory maps was also associated with pain reduction and improved tactile discrimination following drug therapy accompanied by graded desensitization and motor tasks (sensory-motor returning treatment) [85]. The extent of re-reorganization associated with the reduction in CRPS pain suggests that pain is related to the extent of neuroplasticity. Although these findings of cortical reorganization and then normalisation following treatment are only correlational, there is some evidence that targeting the

cortical reorganization itself might reduce pain and other symptoms of CRPS. Cortical changes have been targeted directly by anodal transcranial Direct Current Stimulation over primary sensory and motor cortex [197,198] or repetitive TMS over the motor cortex [199–201]. Both of these interventions resulted in promising analgesic effects in chronic pain, including CRPS in preliminary studies, although the abovementioned studies have not tested whether they actually reverse cortical reorganization.

Compared to direct efforts to induce cortical reorganization, the research on behavioural methods addressing neuropsychological deficits in CRPS has been more extensive. Several therapies, such as mirror therapy, graded motor imagery, and prism adaptation, appear to have beneficial effects on both the neuropsychological and clinical symptoms of CRPS. Mirror visual feedback therapy [202] relies on correcting the mismatch between motor commands and sensory feedback. This method reduced pain and other symptoms, and improved motor function of the affected limb, in people with CRPS with [203–205] and without [46,206] neurological injury. In Graded Motor Imagery, hand laterality recognition training and imagined hand movements are thought to sequentially activate cortical motor networks without requiring real movements, and thus reduce movement-related pain that might be associated with mirror therapy [207–209]. This treatment decreased pain and oedema, and reduced the speed of limb laterality recognition in CRPS (although one study failed to replicate the effect of pain reduction [56]). Mirror visual feedback and Graded Motor Imagery can also reduce pain and improve motor function in other chronic pain conditions, particularly phantom limb pain [207,210,211]. Prism adaptation [212,213], adapted from rehabilitation of post-stroke neglect, is hypothesised to normalise attention bias and / or the sensory-motor integration system in CRPS. In small uncontrolled studies it has been shown to reduce subjective body midline bias, body representation distortions, and pain; and improve autonomic symptoms and motor function in CRPS [55,69,214] (see [215], Chapter 3, for a protocol for a randomised controlled trial). Neurorehabilitation has certain advantages over analgesic medications and brain stimulation. For example, it is easily accessible, inexpensive, is not associated with severe side effects, and can be self-administered. However, the neurorehabilitation techniques discussed above are not alternatives to other rehabilitation methods. Instead, they could be used as adjunct therapies to drug treatment, physical / functional therapy, and brain stimulation. Reducing clinical signs such as pain and motor impairment, and cognitive symptoms such as body representation distortion, can help overcome pragmatic barriers in engaging with traditional rehabilitation.

4.5. Summary of clinical relevance of neuropsychological changes

To summarise, supraspinal mechanisms appear to contribute to CRPS symptomatology on the level of cognitive functions. This is demonstrated by spatial and multisensory modulation of sensory, motor, and autonomic function; and evidence that the extent of neuropsychological changes is related to pain severity. There is emerging support for targeting neuropsychological

deficits to relieve physical symptoms of CRPS. Neuroimaging studies indicate that cortical reorganization in CRPS can be reversed, although thus far, no study has investigated if this reversal is accompanied by any cognitive changes. Conversely, it remains unclear whether neurocognitive treatments reduce the clinical symptoms of CRPS through reversing cortical reorganization, or through changes on a behavioural level (or both). In particular, there is currently no neuroimaging research on whether any functional reorganization in parietal networks (implied by neuropsychological changes) relates to clinical manifestations of CRPS. Despite the promising effects of emerging neurorehabilitation strategies, their working mechanisms are yet to be fully understood, and the quality of evidence supporting their implementation in standard clinical practice is still insufficient. One potential avenue towards developing new treatments could involve taking advantage of intact cognitive functions. For example, the rubber hand illusion [41] could be used to work towards tolerating touch on the affected limb while observing touch on the artificial limb, and altered auditory feedback [48] could be used during auditory-motor adaptation to improve movement of the affected limb.

5. Conclusions and outstanding questions

Overwhelming evidence of neuropsychological alterations warrants their consideration in the management of CRPS along with the sensory, motor, and autonomic symptoms. Although posttraumatic aberrant inflammatory response can explain several symptoms of CRPS, changes in the central nervous system might better account for these once the peripheral processes subside. The role of cortical mechanisms in CRPS is evident in the neuropsychological symptoms, modulation of low-level sensory and autonomic symptoms by higher cognitive functions (see Table 4), and functional cortical reorganization. Neuropsychological changes found in CRPS include distorted body representation, deficits in lateralised spatial cognition, and impairment of other non-spatially-lateralised cognitive functions (see Table 2). They appear to pertain to manifestation of this syndrome and relate to its clinical outcomes, such as pain. Here we provide several concluding remarks and lay out suggestions for further research to investigate the cognitive aspects of CRPS and other chronic pain syndromes.

1) The “neglect-like” framework does not fully capture the neuropsychological changes found in CRPS. Instead, disruption to the parietal cortical network might provide a better framework for characterising these symptoms. This would incorporate “neglect-like” symptoms that are often reported in CRPS (which in hemispatial neglect are often associated with temporo-parietal right hemisphere lesions [109–111]). But the parietal framework would also include other changes in spatial cognition that are not consistent with reduced attention to the affected relative to unaffected side (e.g. the shift of the egocentric reference frame towards the affected side [68,70], or a leftward spatial bias regardless of which side is affected by CRPS [40,66]). The posterior parietal cortex has been implicated as a crucial area for constructing spatial representations of the body and external space, as well as body ownership [104,216–219].

Other cognitive changes reminiscent of parietal deficits that have been seen in people with CRPS include impaired non-spatially-lateralised constructional and gnostic abilities [65,71,220], although some parietal functions such as multisensory integration might be intact [41,104]. Overall, combined evidence of abnormal lateralised spatial cognition, body representation, and non-spatially-lateralised cognitive functions in CRPS suggests that functional reorganization of the parietal cortex could underlie the manifestation of neuropsychological symptoms in CRPS. Further neuroimaging studies could test whether functional alterations in parietal cortex indeed correlate with observed neuropsychological symptoms to complement the behavioural findings.

2) Neuropsychological symptoms might not all be specific to CRPS, but instead could have ramifications for understanding the cognitive aspects of other chronic pain conditions and applying neurocognitive treatments that are beneficial for CRPS to these disorders. Chronic pain in general can impair cognitive functions such as memory, attention, or executive function, and these impairments have been linked to pain intensity [95,193]. There are some cognitive changes that distinguish CRPS from other unilateral limb pain syndromes (such as arthritis or neuropathic pain [35,70,186]). Nonetheless, some neuropsychological symptoms are seen across these different pain disorders as well as in people with non-lateralised and widespread pain (such as chronic back pain or fibromyalgia) [190]. There are groups of chronic pain syndromes that are associated with plastic changes in the central nervous system, including phantom limb pain, fibromyalgia, and CRPS [221]. People with these conditions can present with similar distortions of body representation and spatial cognition (e.g. [62,145,190,222,223]), which inspired therapeutic approaches targeting these symptoms to reduce pain [224].
3) Striking findings that cortical reorganization in CRPS can be reversed after recovery [85,196] suggest that the central mechanisms of chronic pain can be targeted for treatment. Recognising similarities between mechanisms and symptomatology of different pain syndromes can facilitate broader applications of treatments that are beneficial in some disorders. Several neurocognitive rehabilitation strategies developed for CRPS, or adapted from other neurological or pain conditions, have provided some relief from pain and other symptoms [69,206,208]. However, there is a need for studies involving larger patient groups and more rigorous controls to better evaluate the benefits of many of these treatments. Another issue is that studies of treatments that target neuropsychological symptoms or cortical networks rarely evaluate the changes in these factors. Identifying the mechanisms of action of neurocognitive treatments, and understanding which neuropsychological symptoms should be targeted for rehabilitation, would help to maximise its therapeutic effects. For instance, not all individuals with CRPS present with the same neuropsychological changes, thus stratified management might be most efficient.

4) Recognising the limitations of the research reviewed in this article and gaps in our understanding of the neuropsychological aspects of CRPS, we would like to put forward some recommendations that could improve further studies on this topic. Even though there is a body of evidence suggesting systematic neuropsychological changes in CRPS that are apparent on a group level, it would be an overstatement to suggest that all people with CRPS present with such symptoms. High variability in the clinical presentation of CRPS [15] also applies to neuropsychological changes, which do not always replicate across different studies. Some studies (including single cases) might have specifically targeted patients with pronounced impairments (e.g. [53,54,65,71]), or have a high proportion of such patients through a combination of random chance and small sample size. This could lead to overestimating certain neuropsychological symptoms in CRPS. Fortunately, there is an increasing tendency to publish null findings, which should allow a more balanced appraisal of the emerging evidence. Although sample sizes in CRPS research are often limited by the availability of people with this rare condition, large-sample, unbiased studies are needed to establish the prevalence of certain neuropsychological changes, and potentially identify the characteristics of subgroups of patients in whom these symptoms are more prominent. This could be achieved by combining research efforts across multiple sites and countries. Longitudinal research tracking cognitive changes throughout the course of CRPS and its recovery could enhance the understanding of how they can contribute to the development and maintenance of the disorder, and how stable they are over time. Future research could focus on whether there are any cognitive changes in paediatric CRPS and how they correspond to those found in adults. Neuropsychological symptoms in CRPS typically do not arise from any brain injury (in contrast to, for example, hemispatial neglect), thus they might be more subtle compared to those seen in neurological disorders. To detect and precisely quantify these symptoms in CRPS, researchers should use sensitive measures (e.g. TOJs). In contrast to some neurological conditions, people with CRPS often have insight into their cognitive problems, especially in body representation. Therefore, self-report measures appear to be useful in capturing these symptoms [35,43]. However, inconsistencies between self-reported disturbances and the same symptoms measured experimentally suggest that we might lack appropriate methods to quantify these changes in a reliable and objective manner. Some studies fail to verify whether observed neuropsychological symptoms are indeed abnormal (see Table 2). Directly comparing the performance of participants with CRPS and matched healthy controls on the same tests allows appropriate quantification of any deviation from what would be considered a normal performance. This is particularly relevant to studying lateralised spatial attention, as a mild leftward bias ("pseudoneglect" [122]) is often found in neurologically healthy participants. Furthermore, routinely including pain control groups would provide insights into which neuropsychological symptoms are unique to CRPS and which are present in other pain conditions as well. This in turn might facilitate our

understanding of any central mechanisms specific to CRPS and the development of more targeted treatments.

In summary, CRPS appears to be associated with complex neuropsychological changes that include distortions in body representation, deficits in lateralised spatial cognition, and non-spatially-lateralised higher cognitive functions. Some of these cognitive changes are reminiscent of other neuropsychological syndromes that can follow brain lesions, and some might be associated with chronic pain. We argue that the hemispatial neglect framework is not sufficient to characterise the higher cognitive functions affected in people with CRPS. Emerging findings suggest that disruption of parietal cortical networks can play a role in the manifestation of these neuropsychological symptoms. Importantly, cognitive changes in CRPS (and potentially other chronic pain conditions) can be targeted for treatment. Further research taken beyond the analogy to hemispatial neglect could provide a better understanding of the neuropsychological components of CRPS and elucidate how cortical changes contribute to clinical symptoms of this debilitating condition.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Chapter 1 – Conclusions

In this chapter, I outlined behavioural evidence of altered body representation, lateralised spatial cognition, and non-spatially-lateralised cognitive functions in people with CRPS. Notably, the current evidence is neither fully consistent, nor does it provide a complete understanding of neuropsychological changes in CRPS. However, integration of findings that suggest either impaired or intact cognitive domains facilitated the discussion about proposed mechanisms of reviewed neuropsychological symptoms. Although Chapter 1 provides a broad range of insights and directions for further investigation, the following points are particularly pertinent to the rest of this thesis.

Among the reviewed neuropsychological changes, those of body representation have been studied most extensively in CRPS. Here, interventions targeting these changes, such as graded motor imagery, have already been integrated into CRPS management practices. The remainder of this thesis, on the other hand, primarily concerns the changes in spatial cognition. One reason for this is that although "neglect-like" symptoms were first reported almost 25 years ago (Galer et al., 1995), it appears that this domain received less attention in subsequent research compared to body representation. Considering the evidence reviewed in this chapter, there appear to be many inconsistencies regarding the prevalence of "neglect-like" symptoms in CRPS, as well as direction and magnitude of spatial biases. Furthermore, experimental research on movement-related spatial biases is sparse. Chapters 2 and 4 will aim to reconcile some of the mixed findings about spatial attention biases in CPRS, and Chapters 4 and 5 will also provide an assessment of motor "neglect-like" symptoms. Further rationale for focusing particularly on spatial cognition in this thesis is its relatively untapped potential for treatment. Considering some neuropsychological similarities between CRPS and hemispatial neglect summarised in this chapter, prism adaptation treatment has been applied to CRPS with promising results. However, we need more robust evidence of the efficacy of prism adaptation for CRPS to be able to make any treatment recommendations. Chapters 3 and 5 will address this gap in the existing literature.

The discrepancies regarding the prevalence of "neglect-like" symptoms in CRPS highlighted in this chapter could arise partly because the researchers had not yet used methods sensitive enough to capture spatial biases in people with chronic pain, which are likely to be subtle because these patients are otherwise neurologically healthy. One common objective across all the following experimental chapters is to quantify spatial biases in CRPS using sensitive measures, drawing from methodology used to measure subtle spatial biases in brain lesioned patients and healthy controls. Chapter 2 will additionally explore the advantages of sensitive computer-based measures versus less sensitive "pen-and-paper" tests of spatial cognition.

In this chapter, I discussed potential mechanisms through which neuropsychological symptoms can arise in CRPS. Considering the manifestation of "neglect-like" symptoms, distorted body

representation and underutilisation of the affected limb, and distinct cognitive representation of near and far space seem particularly relevant. Chapter 2 will investigate these proposed mechanisms of spatial biases in CRPS.

Another key question highlighted in the literature review was whether higher cognitive functions contribute to the clinical signs of CRPS. This chapter demonstrated that sensory, autonomic, and motor functions can be modulated by spatial or multisensory manipulations, implying the role of cognitive representations of space in the manifestation of clinical signs of CPRS. Furthermore, neurocognitive treatments were found to relieve CRPS symptoms. There is also evidence linking the severity of neuropsychological symptoms to severity of pain and other signs of CRPS, yet these relationships are not consistently found. In Chapters 2, 4 and 5 I will further explore potential associations between neuropsychological functions and clinical manifestations and treatment of CRPS.

This literature review revealed that most previous research on neuropsychological functioning in CRPS is limited by small sample sizes, lack of control groups or conditions, and paucity of longitudinal assessments. While comprehensive case studies, such as the one I will present in Chapter 2, can provide important proof of concept of potential mechanisms of the neuropsychological symptoms, underpowered and uncontrolled group studies might lead to overestimation of the neuropsychological deficits or exacerbate replication problems. In this thesis, I will avoid these limitations by testing a relatively large cohort of people with CRPS given the syndrome's rarity (Chapters 4 and 5). I will also use healthy individuals as a reference against which any cognitive deviations in people with CRPS can be assessed (Chapters 2 and 4). Furthermore, I will include a control treatment condition to assess the "true" effects of prism adaptation on CRPS in a double-blind randomised trial (Chapter 5). Finally, I will provide a longitudinal assessment of neuropsychological functions in CRPS (Chapters 2 and 5) allowing to examine their consistency over long periods of time.

Chapter 2: Attention upturned: Bias toward and away from the affected side of the body and near space in a case of Complex Regional Pain Syndrome

Chapter 2 – Introduction

This chapter presents a case study of a woman with CRPS affecting her left wrist, who has previously presented to our laboratory with reduced attention to and distorted representation of her affected limb. This patient's neuropsychological symptoms were unusual in that they were more severe than is usually found in people with CRPS and therefore more closely resembled what is typically shown by patients with hemispatial neglect after brain injury. This extreme case of neuropsychological symptoms in the absence of any brain lesions presented an opportunity to disentangle some of the proposed mechanisms of spatial attention biases in CRPS that were discussed in Chapter 1 (e.g. that these biases are driven by body perception, reduced movement in the affected side of near space, or distinct cortical representations of near and far space). Any dissociations between the regions of space or tested modalities in which attention biases manifest should be more apparent in such a single case than in a heterogeneous group of individuals with CRPS. The current work was prompted by this patient's unusual symptoms in a previously published group study (Bultitude et al., 2017). Hence, I include her individual data collected as part of that study as the first research session in this chapter. I believe this is appropriate because the emphasis of the previously published work was on comparisons of group-averaged data rather than individual data, and presenting this patient's individual data from this session in the current case study is necessary for illustrating the development of her spatial attention bias over time. Independent of the group study by Bultitude and her colleagues (2017), I present a comprehensive examination of this patient over two further research sessions.

The second session aims to confirm that the patient does not have generalised cognitive deficits that could account for her impaired performance on spatial attention tests. To follow up on the problem I identified with the sensitivity of available methods used to test spatial attention bias in CRPS (Chapter 1), I also investigate if her severe spatial attention biases are apparent on standard confrontation testing and "pen-and-paper" tests of neglect (i.e. Behavioural Inattention Test battery). This enables me to evaluate her performance on tests of spatial cognition with different degrees of sensitivity. I also test whether her performance on spatial attention tasks in the first session can be explained by response bias (i.e. a preference for reporting the stimuli on her unaffected side due to aversion to her affected side). Response bias has rarely been considered or controlled for in previous studies of spatial bias in CRPS, despite evidence that patients can have aversions to words that they associate with their affected limb that might elicit such a bias.

To expand on the findings from the first research session, I further quantify the patient's visual attention biases in body (personal) space and near space using an adjusted temporal order judgement task. Assuming that spatial attention biases are driven by distorted representation of the affected limb, they should be more severe in body than near space. Furthermore, if limited action of the affected limb contributes to spatial attention deficits, the latter should be stronger in near space where most movements are performed, compared to the far space, which extends beyond one's reach. Thus, I test her attention in these three regions of space. This session also examines any biases in mental representation of space (independent of body representation and movement), presence of which would suggest generalised impairment of spatial cognition. Moreover, in Chapter 1 I suggested that neuropsychological symptoms in CRPS (including spatial attention biases) could be driven by cortical reorganisation in similar networks to those that are disrupted in individuals with hemispatial neglect. In this case, the CRPS patient might also present with other symptoms typical of right-hemisphere disturbance (contralateral to her affected limb), such as a bias towards processing of local relative to global level of information.

The third research session aims to address several outstanding questions. To further investigate the potential impact of underutilisation of the affected limb on spatial attention, I test whether visual attention bias differs between two vertical regions of near space: hands working space and near space of eye level. To quantify any tactile spatial biases, suggested by the patient's performance on confrontation tests, I also administer a tactile temporal order judgement task. Moreover, this session examines if any local relative to global processing biases can be quantified using a task adjusted for the patient's visual acuity. Finally, I assess whether the patient's spatial attention biases can be explained by any primary lateralised visual or somatosensory deficits.

Overall, the investigations in this chapter allow me to characterise the conditions under which spatial attention biases can manifest in CRPS, control for several potentially confounding factors (e.g. response bias, visual acuity loss) that are rarely (if ever) considered in other studies of CRPS, and explore potential mechanisms of spatial bias based on known dissociations identified in post-stroke neglect patients.

Statement of authorship

This declaration concerns the article entitled:			
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Candidate's contribution to the paper (provide details, and also indicate as a percentage)	Monika Halicka considerably contributed to this study (70%), being involved in formulation of ideas (65%), design of methodology (70%), experimental work (65%), and presentation of data in journal format (90%).		
Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.		
Signed	Monika Halicka	**Date**	10.05.2020

Attention upturned: Bias toward and away from the affected side of the body and near space in a case of Complex Regional Pain Syndrome

Monika Halicka[1,2]*, Axel D Vittersø[1,2,3], Michael J Proulx[2,4], Janet H Bultitude[1,2,5]

[1]Centre for Pain Research, University of Bath, Bath, United Kingdom

[2]Department of Psychology, University of Bath, Bath, United Kingdom

[3]Department of Sport and Health Sciences, University of Exeter, Exeter, United Kingdom

[4]Centre for Reality & Virtual Environments Augmentation Labs, Department of Computer Science, University of Bath, Bath, United Kingdom

[5]Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), University of Oxford, Oxford, United Kingdom

***Corresponding author**

Monika Halicka, mon.halicka@gmail.com

Department of Psychology

University of Bath

Claverton Down Road

Bath BA2 7AY

United Kingdom

Data Availability Statement

The data underlying the results presented in the study are available on the Open Science Framework. URL: https://osf.io/5dy3y/ DOI: 10.17605/OSF.IO/5DY3Y

Declaration of interest

The authors have no potential conflict of interest to declare.

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Abstract

Objective: People with Complex Regional Pain Syndrome (CRPS) can show inattention to their affected limb and its surrounding space, resembling post-stroke hemispatial neglect. Although this inattention appears to relate to physical signs of CRPS, little is known about the specific conditions under which it manifests. **Method:** In this case study of a woman with CRPS in her left arm, we tested spatial attention to different regions of space across three sessions spanning three years. **Results:** The patient showed visual and tactile neglect and extinction on her affected side on confrontation tests, but no attention deficits on "bedside" tests of neglect. On sensitive experimental measures, attention biases were found in the patient's body and near space (in Temporal Order Judgements), but not far or imagined space (on the Greyscales task and Mental Number Line Bisection). Unique to the current literature, the patient showed a reversal in her Temporal Order Judgement bias from inattention (first and second session) to hyperattention (third session) to her affected side. Its direction might be independent of pain and body representation distortion, which were similar across the three sessions. **Conclusions:** Spatial attention bias in CRPS can generalise across different sensory modalities and extend beyond the affected limb to the external space around it. This bias is not necessarily directed away from the affected side or stable over time. Present findings support the conclusion that people with CRPS can demonstrate neuropsychological changes, and have potential implications for treatments of CRPS that target attention biases.

Keywords

Complex Regional Pain Syndrome; spatial attention; temporal order judgement; body representation; hemispatial neglect

Key points

Question: Similar to patients who had a stroke, people with certain chronic pain conditions can pay less attention to the affected side of their body, yet little is known about how such shifts in attention manifest in the absence of brain damage. **Findings:** A patient with chronic pain in her left arm showed altered attention to her body and the external space within her reach, however, the direction of attention bias shifted over time from reduced to increased attention to her affected side, despite no changes in pain intensity and cognitive representation of her body. **Importance:** Treatments that aim to bring the attention back to the affected side to reduce chronic pain must consider that attention shift may not be stable over time or related to pain, and that its direction can vary among patients. **Next steps:** Further research should investigate longitudinal changes in attention and their prevalence in chronic pain, and explore their underlying neural mechanisms.

1. Introduction

Complex Regional Pain Syndrome (CRPS) is characterised by pain, sensory and motor abnormalities, swelling, temperature changes, and trophic alterations in one or more limbs. This chronic pain disorder typically arises following a trauma to the limb; however, the pain and other symptoms are disproportionate to any inciting injury. People with CRPS can present with distorted body representation (Lewis & McCabe, 2010; Lewis & Schweinhardt, 2012), and changes in attention to their affected limb and its surrounding space that resemble hemispatial neglect ("neglect") following a brain lesion (Legrain et al., 2012; Punt et al., 2013; Torta et al., 2016). The distorted representations of body and near space could be interrelated with pain in CRPS. For example, placing the affected limb in the unaffected side of space reduced pain and increased subjective limb ownership (Moseley et al., 2012). Pain intensity also predicted the magnitude of spatial bias in processing body relevant information in the affected side of space (Reid et al., 2016). These changes in bodily and spatial representations might contribute to the development and maintenance of CRPS (Bultitude & Rafal, 2010; Marinus et al., 2011; McCabe & Blake, 2008; Sumitani, Rossetti, et al., 2007), and treatments targeting them can relieve symptoms (Bultitude & Rafal, 2010; Christophe, Chabanat, et al., 2016; Sumitani, Rossetti, et al., 2007). Therefore, it would be beneficial to gain a better understanding of the circumstances under which such changes can arise and the extent to which they resemble known conditions such as neglect.

To this end, we conducted a case study of a woman with CRPS who presented with signs of inattention to her affected left limb and body representation distortion in our previous study (Bultitude et al., 2017). Her attention bias was more pronounced than for any other patient tested and, unusually for CRPS, manifested in confrontation testing, reminiscent of post-stroke neglect. Although people with CRPS often report "neglect-like" symptoms regarding the affected limb (Frettlöh et al., 2006; Galer et al., 1995), they usually do not show attention deficits on classic "bedside" tests of neglect (Christophe, Chabanat, et al., 2016; Förderreuther et al., 2004; Kolb et al., 2012; Reid et al., 2016; Reinersmann et al., 2012), with rare possible exceptions (Cohen et al., 2013; Robinson et al., 2011). Yet subtle changes have been reported when more sensitive measures of attention are used (Bultitude et al., 2017; Filbrich et al., 2017; Moseley et al., 2009). This patient's particularly strong attention bias presented an opportunity to test specific predictions about how attention bias can manifest in CRPS, since any differences between tested conditions would be more apparent, whereas potential dissociations between spatial biases might easily be lost in a group study due to the heterogeneity of CRPS (Caramazza, 1986). Therefore, we conducted a case study over two further sessions to evaluate the nature of this patient's spatial attention deficits with respect to different regions of space and sensory modalities. Although it was not our objective to demonstrate what is typical of general CRPS population, a case study of a patient with strong signs of neglect could guide further research regarding the

neuropsychological changes in CRPS and their causes. Furthermore, examination of the patient's unique cognitive and sensory changes bears theoretical relevance to understanding how spatial attention can be disrupted in the absence of brain damage.

In contrast to CRPS, lateralised spatial attention deficits in post-stroke neglect have been extensively described. They can manifest across different regions of space and sensory modalities (Kerkhoff, 2001; Vallar, 1998). Furthermore, dissociations between neglect of body and external space (Committeri et al., 2007; Guariglia & Antonucci, 1992), near and far space (Aimola, Schindler, Simone, & Venneri, 2012; Cowey, Small, & Ellis, 1994; Halligan & Marshall, 1991; Keller, Schindler, Kerkhoff, Rosen, & Golz, 2005; Vuilleumier, Valenza, Mayer, Reverdin, & Landis, 1998), perceptual and motor performance (Bisiach et al., 1990; Buxbaum et al., 2004; Liu et al., 1992), and different senses (Barbieri & De Renzi, 1989; Bisiach et al., 2004; Cubelli et al., 1991; Marsh & Hillis, 2008), have been also found. Here we sought to determine if some such classic dissociations identified in post-stroke neglect also arise in CRPS, with a view to understanding the mechanisms through which attention can come to be altered in this population. Specifically, we (1) used confrontation tests, "bedside" tests of neglect, and experimental measures to study spatial attention across different modalities in body space (vision and touch), near and far space (vision), and imagined space (mental representation); (2) tested for potential response biases and hemisensory deficits to rule out alternative explanations of lateralized attentional biases; and (3) examined cognitive biases typical of right hemisphere damage that often co-occur with post-stroke neglect. The background evidence and rationale for the above objectives are outlined below.

In healthy individuals, nociceptive stimulation on one side of the body can bias visual attention towards the corresponding side of near space (Filbrich et al., 2016), yet the relationships between chronic pain and spatial cognition appear to be more complex. There is some conflicting evidence regarding the direction of attention bias in CRPS (Moseley et al., 2009; Sumitani, Rossetti, et al., 2007), and in which regions of space and sensory modalities it can be present (Filbrich et al., 2017). Judgements of the subjective body midline that require relating the orientation of one's body to visual stimuli presented in far space, tend to be biased towards the CRPS-affected side (Christophe, Chabanat, et al., 2016; Jacquin-Courtois et al., 2017; Sumitani, Rossetti, et al., 2007; Sumitani et al., 2014; Uematsu et al., 2009). Processing of visual or tactile stimuli in near (Bultitude et al., 2017; Filbrich et al., 2017) and body space (Bultitude et al., 2017; Moseley et al., 2009, 2012), on the other hand, tends to be biased in the opposite direction. It is unclear whether these conflicting findings reflect an underlying neuropsychological diversity in CRPS, and / or if the spatial biases change over time or with recovery. Thus far, few studies tested attention in near and far space in the same CRPS patient(s) using the same tasks, with the exception of Filbrich et al. (2017), who found a visual attention bias away from the affected side when stimuli were presented next to the hands, but not when they were presented at a greater

distance from the body, out of reach. The present study aimed to test the direction and magnitude of the patient's spatial attention biases in body (personal) space, near hands working space and near space on eye-level, and far space, across three sessions.

These particular regions of space were drawn from existing evidence in the post-stroke neglect and CRPS literature, as outlined below. One attempt to conceptualize why attention bias in CRPS could vary across space links to its relationship to distorted body representation (Bultitude et al., 2017; Lewis & Schweinhardt, 2012; Moseley, 2005; Schwoebel et al., 2001). It has been shown that the extent of body perception disturbance predicts the visual spatial attention bias in CRPS patients (Bultitude et al., 2017), and that spatial deficits are most evident on measures which involve body-relevant information (Reid et al., 2016). Specifically, "somatospatial inattention" hypothesis (Reid et al., 2016) postulates that attention bias should be more pronounced within the interactions between body and near space. This hypothesis prompted investigating whether our patient's attention bias would be stronger in body space compared to near space. Alternatively, some have argued that attention bias might be driven by a limited amount of action in the affected side of near space (Punt et al., 2013), consistent with previous evidence that spatial perception in near space is shaped by one's actions within it (Makin et al., 2010). Most proximal hand movements are performed in near space, whereas CRPS symptoms include motor impairments, such as weakness, limited range of movement, or dystonia of the affected limb. Both the "somatospatial inattention" and action-related theories lead to the prediction that attention bias away from the affected side should be limited to near space - where the hands can be located – compared to far space. Furthermore, people generally perform most daily tasks that involve hand movements in the region of near space inferior to their eye level (e.g. at desk or table level). Considering that there are distinct mechanisms for attention to the inferior (stronger neglect) and superior (stronger pseudo-neglect) part of the visual field (Làdavas et al., 1994; McCourt & Jewell, 1999; Pitzalis et al., 1997), and attention bias in CRPS may be action-driven, we tested spatial attention in hands working space as well as at eye level within near space.

In addition to representations of the body and external space, there is also evidence that spatial biases can manifest in mental representations. Indeed, neglect of the contralesional side of imaged space was previously found in stroke patients (Priftis et al., 2006; Rossetti et al., 2004; Zorzi et al., 2002, 2006), and similar changes have been reported in CRPS (Christophe, Delporte, et al., 2016; Jacquin-Courtois et al., 2017; Sumitani et al., 2014). Importantly, attention in imagined space can be biased in the opposite direction to subjective body midline judgements in far space in the same CRPS patients (Sumitani et al., 2014). An unusual case of hyperattention to the affected side, consistent across near, far, and imaged space, has also been reported (Christophe, Delporte, et al., 2016; Jacquin-Courtois et al., 2017). It is conceivable that the biases in the representations of real and imagined space might be driven by distinct mechanisms, e.g., mental representations could be unaffected by movement of the affected limb, in contrast to biases in

near space. This study therefore investigated the patient's spatial bias in imagined space and whether it would be consistent with other perceptual biases.

Primary experimental evidence of spatial attention biases in CRPS was derived from temporal order judgements in the tactile modality (Moseley et al., 2009, 2012; Reid et al., 2016), and was further corroborated by similar studies in vision (Bultitude et al., 2017; Filbrich et al., 2017). Post-stroke neglect generalized across different senses is a well-documented phenomenon (Bisiach et al., 1985; Weintraub & Mesulam, 1987), which would support supramodal mechanisms of spatial attention (Kinsbourne, 1970). However, commonly found dissociations between visual and tactile neglect (Barbieri & De Renzi, 1989; Bisiach et al., 2004; Marsh & Hillis, 2008) would suggest involvement of independent, modality-specific attentional mechanisms (Rizzolatti & Camarda, 1987). Similar dissociations have been found in CRPS, whereby patients displayed signs of visual, but not tactile inattention to their affected side, implying modality-specific attentional deficits (Filbrich et al., 2017). Our objective was to test if neglect in vision generalizes to tactile processing, especially considering that the latter inherently entails body-relevant information.

When investigating spatial attention, it is important to control for potential confounding factors. For example, spatial attention deficits are prone to over-estimation if response biases are not controlled for (Spence & Parise, 2010). Considering that body representation distortion in CRPS can involve misoplegia-like symptoms, such as aversion, disgust, and hostility towards the affected limb and concepts related to that limb (Bartolomeo et al., 2017; Critchley, 1974; Lewis et al., 2007), it is likely that verbal left/right judgements could introduce a bias in the perceptual estimates. Response bias in this case would entail a preference of one verbal response over the other (e.g. preferring to say "right" when the left limb is affected) when uncertain about spatial judgements. A second type of possible confounding factor when measuring attention bias in CRPS are hemisensory deficits, which are known to extend beyond the CRPS-affected limb (Rommel et al., 1999). Similar to how one would account for hemianopia or hemiplegia when testing for neglect in post-stroke patients, it is important to assess potential sensory deficits that could impair the ability to see or feel stimuli on the CRPS-affected side relative to the non-affected side. In this study, we aimed to separately account for attentional and response biases, as well as hemisensory deficits.

Neglect is not the only cognitive syndrome occurring after right hemisphere lesions. Patients often present with associated disorders such as asomatognosia (impaired awareness or recognition of a body part; Bartolomeo et al., 2017); and deficits in sustained and selective attention, spatial working memory (Van Vleet & DeGutis, 2013), and temporal resolution (Battelli et al., 2001). Right hemisphere lesions are also typically associated with a bias towards processing of local information relative to the global forms, which can be more pronounced for stimuli presented in the contralesional visual field (Bultitude et al., 2009; Lamb et al., 1990; Robertson et al., 1988). Some of these cognitive symptoms have been previously found in CRPS (i.e., impaired finger

identification, Cohen et al., 2013; Förderreuther et al., 2004; and temporal acuity, Bultitude et al., 2017; Filbrich et al., 2017), suggesting that spatial attention bias could be one aspect of broader changes to right hemisphere functioning. In the context of previous evidence of neuroplasticity affecting the hemisphere contralateral to the CRPS-affected limb (Di Pietro et al., 2013b; Juottonen et al., 2002; Maihofner et al., 2003; Pleger et al., 2006; Vartiainen et al., 2008), we aimed to determine if our left-CRPS patient presents with cognitive changes consistent with right hemisphere dysfunction (Bultitude et al., 2009; Navon, 1977) other than "neglect-like" symptoms, such as biased processing of local object features, relative to global forms (Robertson et al., 1988).

To summarize the hypotheses set out in the current investigation, we predicted that the patient's attention deficits would manifest on "bedside" tests of neglect and confrontation tests, in addition to sensitive experimental measures of attention. We further hypothesized that the patient would show inattention to her affected side in different regions of space (body-, near-, and imagined space, but not far space). We predicted that attention bias would be stronger in body (i.e. personal) space compared to near space, stronger in near hands working space at table level compared to near space on eye level, and absent or reversed in far space compared to near space. We further hypothesized that visual neglect would generalize to touch. We expected that the patient would show a response bias in spatial judgements (i.e. reluctance to give the verbal response "left", which refers to her affected side), but that attention bias would be seen even when response bias was accounted for. We similarly examined potential sensory deficits to rule out alternative explanations for the spatial biases. Finally, we hypothesized that the patient would present with a local processing bias.

2. Materials and methods

2.1. Design

We tested the patient's spatial attention over three sessions spanning three years. The first session (T1) was part of our previously published group study of 24 people with CRPS that provided evidence for a visual attention bias away from the affected side of space (Bultitude et al., 2017). Although results from this session have been reported previously, relevant information from T1 is included in this article so that we can provide a complete overview of the development of the patient's performance over time. The second session (T2; pre-registered at osf.io/zx8ad) took place 27 months after T1, and the third session (T3; pre-registered at osf.io/n6qgv) was conducted 10 months after T2 to address outstanding questions. The spacings of the research sessions were determined pragmatically, dependant on the timeline of finalising the design and pre-registrations of T2 and T3, and the researchers' and the patient's availability and ability to travel to the University for testing.

On each occasion, the patient completed self-report questionnaires regarding pain, body representation, fear of movement, and handedness. Across the three sessions, we also tested her attention to different regions of her body and space using three groups of measures: (1) confrontation tests of visual, tactile, and motor neglect and extinction; (2) classic neuropsychological "bedside" tests of neglect; and (3) sensitive experimental measures of attention, including Temporal Order Judgements (TOJs), Greyscales task, Mental Number Line Bisection, and a Global-Local Processing task. Finally, the patient underwent tests of her sensory functions, including central and peripheral visual field acuity, and tactile detection and discrimination thresholds. The timing of the administration of each measure is presented in Table 1. Note that examining any changes in the neuropsychological functions over time was not an *a priori* objective of this study. The consecutive sessions rather aimed to test distinct hypotheses and address the new research questions arising from the preceding assessments. Therefore, majority of administered tests is not consistent across all three sessions. Groups of control participants also completed questionnaires about body representation and handedness, experimental measures of attention, and sensory tests. Written informed consent was obtained from all participants and the study was approved by Oxford A Research Ethics Committee (12/SC/0557).

Table 1 *Test administration across three sessions*

Measure	**T1**	**T2**	**T3**
Self-report questionnaires			
Brief Pain Inventory, BPI (Cleeland, 1996)	●	●	●
Pain Detect Questionnaire, PDQ (Freynhagen et al., 2006)	●	●	●
Edinburgh Handedness Inventory, EHI (Oldfield, 1971)	●	●	●
Tampa Scale for Kinesiophobia, TSK (Miller et al., 1991)	●	●	●
Profile of Mood States, POMS (McNair et al., 1971)	●		
Revised Life Orientation Test, LOTR (Scheier et al., 1994)	●		
Bath CRPS Body Perception Disturbance Scale, BPDS (Lewis & McCabe, 2010)	●	●	●
General cognitive assessments			
Montreal Cognitive Assessment, MoCA (Nasreddine et al., 2005)		●	
Animal semantic fluency (Goodglass & Kaplan, 1983)		●	
Calculation		●	
Sensory tests			
Mechanical Detection Thresholds, MDT (Rolke et al., 2006)			●
Two-Point Discrimination, TPD			●
Freiburg visual acuity test, FrACT (Bach, 1996)		●	

Measure	**T1**	**T2**	**T3**
RareBit Perimetry (Frisén, 2002)			●
Landolt C test			●
Confrontation tests			
Visual neglect / extinction	●	●	●
Tactile neglect / extinction		●	●
Motor neglect / extinction		●	
Neuropsychological "bedside" tests of neglect			
Behavioural Inattention Test battery (Wilson et al., 1987)		●	
Bells cancellation (Gauthier et al., 1989)		●	
Fluff test (Cocchini et al., 2001)		●	
Room description (Zoccolotti & Judica, 1991)		●	
Experimental measures of attention			
Visual Temporal Order Judgement, TOJ (Bultitude et al., 2017) – Uncrossed Hands	●	●	
Visual TOJ – Crossed Hands	●	●	
Visual TOJ – Board	●	●	●
Visual TOJ – Wall			●
Tactile TOJ – Knees			●
Greyscales task (Nicholls et al., 1999)– Near		●	●
Greyscales task – Far		●	
Mental Number Line Bisection (Sumitani et al., 2014; Zorzi et al., 2002)		●	
Global-Local Processing task (Bultitude et al., 2009; Navon, 1977)		●	●

Note. T1 = Session 1; T2 = Session 2; T3 = Session 3.

2.2. Participants

2.2.1. Case summary

The patient was a right-handed woman, aged 63 years at T1, with CRPS affecting her left arm for eight years. Due to a fall, she suffered multiple fractures and dislocations to her left wrist, arm, and shoulder, requiring surgery and seven weeks of cast immobilisation. She reported experiencing "excruciating burning pain" and sensory disturbances in her left arm during post-operative recovery (e.g., feeling and hearing the fingers of her injured hand scratching a pillow, although they were not touching it), as well as tightness of the cast in the weeks that followed. Her description of the period following the injury suggests distorted body representation, that is, her left arm felt bigger, heavier, and misshapen, she had difficulty recognising her arm, and found mirror visual feedback therapy (McCabe, 2002) very confusing. The patient described the inciting injury as a traumatic experience and presented with a reluctance to look at her affected limb and

aversion to certain associated words (e.g., "left", and "wrist", preferring to use the term "the base of the forearm"). In T2, we observed that she was reluctant to look at her affected limb, in particular when it was uncovered (the patient kept her left wrist covered in a bandage, but agreed to remove it for the time of the assessments). She expressed a desire to amputate the left arm, accompanied by feelings of disgust, and at the same time described and exhibited strong guarding and protective behaviours towards that arm. For instance, she reported wearing a make-shift sling and intentionally walking with her left side facing the buildings or walls to avoid anyone touching her affected arm. In T2, we also observed that the patient kept her left arm close to her chest while walking. However, in T3, she was no longer wearing a sling. Self-report measures across three sessions indicate that her body representation was severely distorted, relative to that of healthy controls (Table 2). For instance, in T2 she described the mental image of her affected hand as "a grotesque blob that has got not necessarily edges to it (…), does not seem to have a definition like the other hand, it is very big in comparison to the unaffected side", and the rest of her arm as "a stick that connects to the blob, just holding it there, but it has a problem supporting itself (…), it is not connected at the top, it is too high up". The patient provided a similar description in T3, which is illustrated in Figure 1. Moreover, her pain-related fear of movement across three sessions was stronger than is usually found in chronic pain patients (Roelofs et al., 2004) (Table 2).

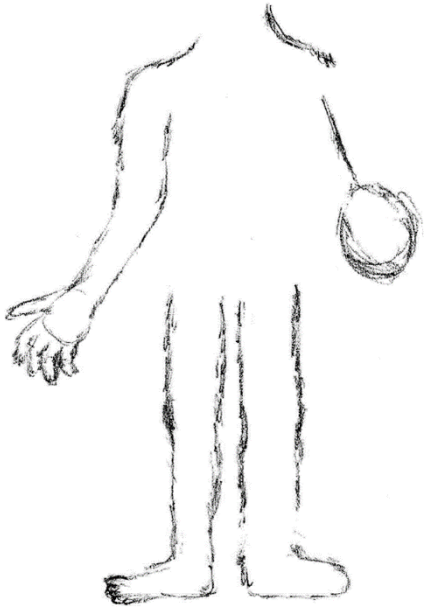

Figure 1. Body representation distortion. A sketch of the patient's cognitive representation of her limbs as she described them during a mental imagery task in T3.

Table 2 *The patient's scores on self-report questionnaires of pain, body representation, and limb use; tests of cognitive functions; and sensory testing*

Clinical / Sensory / Cognitive tests	**Measure**	**Patient's score**		
		T1	**T2**	**T3**
Pain severity	BPI (Cleeland, 1996) – severity (/10)	7.75	8.25	7.00
Pain interference with daily life	BPI (Cleeland, 1996) – interference (/10)	8.28	7.00	7.86
Neuropathic pain component	PDQ (Freynhagen et al., 2006) (/38)	29[a]	35[a]	27[a]
Recalled handedness before CRPS	EHI (Oldfield, 1971) (-100 to +100)	100	73	-[b]
Current handedness	EHI (Oldfield, 1971) (-100 to +100)	100	100	100
Pain-related fear of movement and re-injury	TSK (Miller et al., 1991) (/68)	45[a]	42[a]	46[a]
Mood disturbance	POMS (McNair et al., 1971) (/200)	104[a]	-	-
Depression	POMS - Depression (/60)	34[a]	-	-
Anxiety	POMS - Anxiety (/30)	26[a]	-	-
Optimism	LOTR (Scheier et al., 1994) (/24)	6[a]	-	-
Body representation	BPDS (Lewis & McCabe, 2010) (/57)	55[c]	55[c]	52[c]
General cognitive functions	MoCA (Nasreddine et al., 2005) (/30)	-	29	-
Semantic verbal fluency	Animal fluency (Goodglass & Kaplan, 1983)	-	22	-
Arithmetic abilities / numerical processing	Calculation[d] (/12)	-	12	-
Tactile detection threshold	MDT (Rolke et al., 2006) – hands[e]	-	-	-6.09[c]
	MDT (Rolke et al., 2006) – knees[e]	-	-	0.50
Tactile discrimination threshold	TPD – hands[e]	-	-	-1.17[c]
	TPD – knees[e]	-	-	-0.98

Note. T1 = Session 1; T2 = Session 2; T3 = Session 3; BPI = Brief Pain Inventory; PDQ = Pain Detect Questionnaire; EHI = Edinburgh Handedness Inventory, scored from -100 (extreme left-handedness) to +100 (extreme right-handedness); BPDS = Bath CRPS Body Perception Disturbance Scale; TSK = Tampa Scale for Kinesiophobia (compared to mean scores of chronic lower back pain and fibromyalgia patients; Roelofs et al., 2004); POMS = Profile of Mood States (compared to mean scores of healthy 60-69 years old adults; Gibson, 1997); LOTR = Revised Life Orientation Test (compared to normative values for healthy 61-70 years old females; (Glaesmer et al., 2012); MoCA = Montreal Cognitive Assessment; MDT = Mechanical Detection Threshold; TPD = Two-Point Discrimination.

[a] Significantly different to normative cut-off score, indicating pathology. [b] Not tested. [c] Significantly different from control participants. [d] Non-standardised measure with arbitrary cut-off score of < 9 correctly resolved mathematic equations indicating arithmetic skills impairment. [e] Calculated as side ratio: [(left-right)/left], where a negative number indicates higher sensitivity (MDT) or better precision (TPD) on the left (affected) side.

In addition to her recounted sensory disturbances in her affected arm, the patient reported double vision and loss of peripheral vision. She reported visiting the optometrist every six months to update her prescription and was using custom-made corrective lenses during each research session. The patient described having problems with balance for several years up to and including

the research sessions. Until inpatient rehabilitation six months prior to T2 she had relied on a crutch to help her walk straight, as she tended to "veer off to the left". At the time of T3, the patient reported that her balance was still impaired and she experienced falls, yet with no need to return to using a crutch. Magnetic Resonance Imaging scans performed two and five years prior to T1 to investigate her problems with vision and balance ruled out any observable lesions or other brain pathologies. Other neurological disorders were also ruled out by a neurologist. Her performance on the Montreal Cognitive Assessment (Nasreddine et al., 2005), Animal Fluency Test (Goodglass & Kaplan, 1983), and a Calculation test in T2 did not indicate any cognitive impairment (Table 2).

The patient reported a history of post-traumatic stress disorder and depression following the inciting injury. No psychiatric evaluation for mood disorders was conducted during the research sessions. However, according to the Profile of Mood States (McNair et al., 1971) and Revised Life Orientation Test (Scheier et al., 1994) completed in T1, the patient's depression and anxiety scores were above, and optimism below, normative values for her age range (Table 2). The patient reported no other neurological or psychological comorbidities.

Pain medications taken at the time of the assessments were tramadol (400mg/day) at T1; gabapentin (2100mg/day), tapentadol (300mg/day), and amitriptyline (75mg/day) at T2 and T3; and aspirin (75mg/day) at T2. The patient had stellate ganglion blocks for shoulder pain approximately once per year (the last one 3 months before T3). She also attended three two-week inpatient multidisciplinary pain management programmes for CRPS (twice between T1 and T2, and once between T2 and T3). The pain management programmes involved physiotherapy, hydrotherapy, occupational therapy, psychological support, patient-centred goal-setting, education about CRPS, and consultation about pain medication.

The patient's CRPS symptoms fulfilled the Budapest research diagnostic criteria (Harden et al., 2010) in each session of the study. She reported severe, persistent pain (Numerical Rating Scale [NRS] T1 = 8; T2 = 8; T3 = 7 / 10) in her left wrist that radiated up to the shoulder (Figure 2). According to the patient's description, the left shoulder also felt heavy, like it was being pulled down. In T2, the patient was not willing to allow the researchers to touch her left wrist and hand due to severe allodynia, however, in T3 she was able to undergo sensory assessments on the affected hand. The only other changes in her physical pain symptoms across the three sessions were that she had pain in her right shoulder in T1 that was not present in T2 or T3, and that she injured her left foot (trip and fall) five months before T3. According to the patient's description, her leg was badly bruised below the knee down to the foot and swollen for several weeks. In T3 the patient reported – in addition to the symptoms in her left arm – discontinuous pain in her left leg (NRS = 5 / 10 at the time of assessment), tingling in the toes of her left foot, difficulty distinguishing between the toes of her left foot, and altered cognitive representation of that limb (Figure 1). The patient also described the left ankle turning inwards and that she used the outside

part of her foot while walking. She disclosed that her General Practitioner attributed these symptoms to peripheral neuropathy. As the pain in her foot was not continuous, it would not meet the Budapest diagnostic criteria for CRPS.

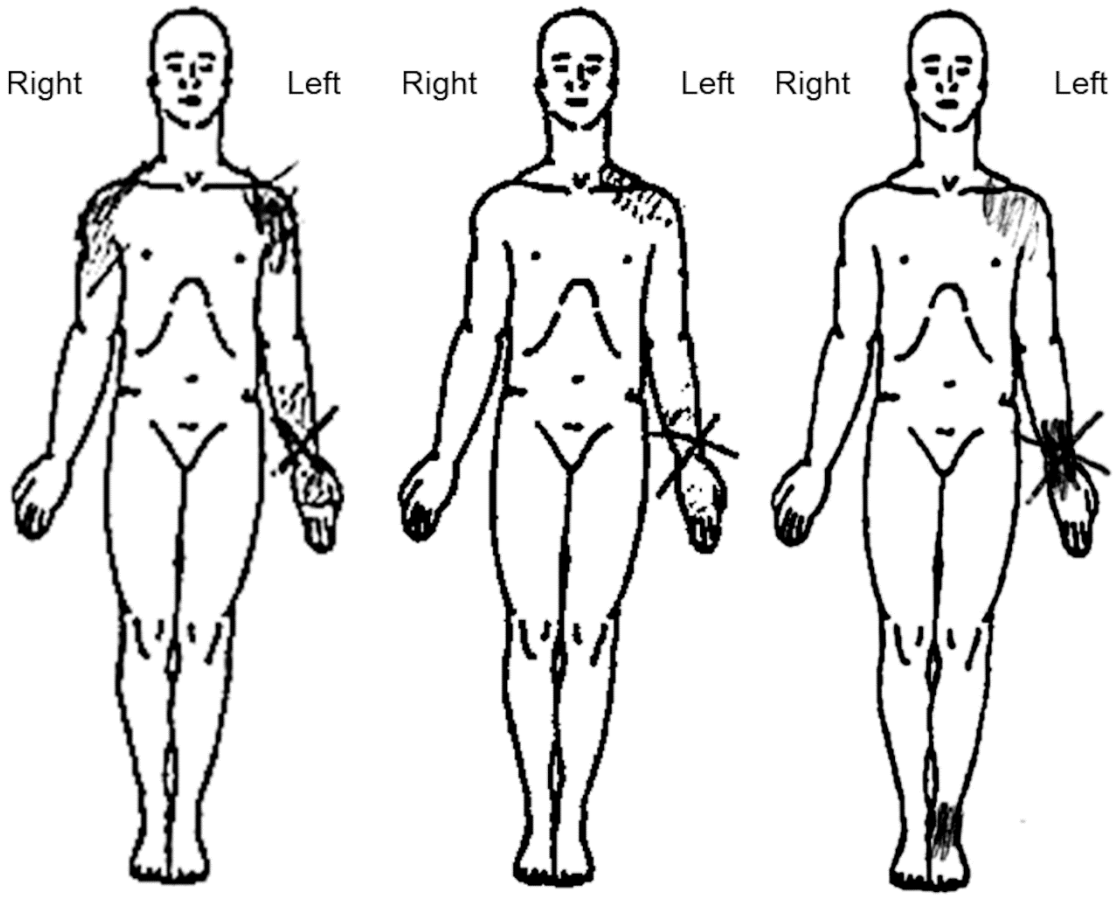

Figure 2. Areas of pain shaded on the body diagrams. Images were taken from the Brief Pain Inventory in T1, T2, and T3 (from left to right, respectively). A cross represents the region of worst pain.

We tested for hemisensory changes on the patient's upper and lower limbs in T3. We used Von Frey filaments to establish mechanical detection thresholds on the hands and knees according to a standardised protocol from Quantitative Sensory Testing (Rolke et al., 2006). The patient had lower detection threshold, i.e. increased sensitivity to touch on the left hand (0.079g) than the right one (0.557g). A staircase assessment of tactile discrimination thresholds on her index fingers and knees was conducted using a Two-Point Discrimination disk (see Supplemental Material). The patient had a lower threshold, i.e. more precise tactile discrimination on the left hand (3.86mm) than right one (8.38mm). Side ratios [(left-right)/left] of the patient's sensory thresholds were significantly different from control participants on the hands, but not on the knees (Table 2), suggesting that hemisensory changes were restricted to the upper (CRPS-affected) limbs.

2.2.2. Control participants

Healthy, pain-free participants with normal or corrected-to-normal vision and no history of neurological disorders were recruited to provide control data for experimental and non-standardised measures. The control samples were in T1: 19 females, 5 males, mean age 46.21 years, *SD* = 14.96, 2 left-handed, 22 right-handed (age- and sex-matched to the group of CRPS patients in the original study; Bultitude et al., 2017); in T2: 12 females, mean age 62.42 years, *SD* = 3.23, all right-handed; in T3: 11 females, 1 male, mean age 50.50 years, *SD* = 13.09, all right-handed. The size of control groups for T2 and T3 was determined to statistically compare data from a single case to a control sample. Crawford and Garthwaite (2005) examined control of the Type I error rate for the Revised Standardised Difference Test (RSDT) through Monte Carlo simulation and found that control samples of $n = 10$ were necessary to limit Type I error rates to 5% or lower. We used samples of $n = 12$ in case any control participants would need to be excluded from individual analyses due to incomplete data. The mean age of control participants was not significantly different from the patient's age across the three sessions ($p = .26$; $p = .46$; $p = .28$, respectively). Despite modest effect of sex differences on visuospatial attention (Jewell & McCourt, 2000), it is unlikely that the inconsiderable number of male participants in the control samples in T1 (5/24) and T3 (1/12) would bias the results of this study.

2.3. Procedures

2.3.1. Confrontation tests

We tested for visual and tactile neglect and extinction using confrontation testing (unilateral or bilateral finger movements or light taps to the knees). The presence of motor neglect and extinction was assessed by asking the patient to lift her left arm, right arm, or both arms, with her eyes open or closed (T2). These tests were performed according to the standard procedures for neurological assessment (Bender, 1952; Karnath et al., 1993) by trained psychologists. Any number of omissions in the patient's performance on the confrontation tests was considered abnormal.

2.3.2. Neuropsychological tests

Classic "bedside" tests of neglect, including the conventional Behavioural Inattention Test battery (Wilson et al., 1987), were administered by trained psychologists. This set of measures comprised tests of visual-motor neglect in near space (e.g., line bisection, bell cancellation; Gauthier, Dehaut, & Joanette, 1989), representational and visual-motor neglect in near space (representational drawing; Wilson et al., 1987), visual neglect in near (article reading; Wilson et al., 1987) and far space (room description; Zoccolotti & Judica, 1991), and neglect in body space (fluff test; Cocchini, Beschin, & Jehkonen, 2001). The results obtained in neuropsychological tests by the patient were compared against available cut-off scores for neglect.

2.3.3. Experimental measures of attention

The type and purpose of all computer-based experimental measures of spatial attention, mental representation of space, and global and local processing are summarised in Table 3.

Table 3 *Summary of the experimental tasks and conditions with operationalization of measured constructs and time points of assessments*

Task	**Condition**	**Time points**	**Measured construct**	**Operationalization**
Visual Temporal Order Judgement (Bultitude et al., 2017)	Uncrossed Hands	T1, T2	Visual spatial attention to body (personal) space and near space (in hands working space). Body and near space are congruent.	Point of Subjective Simultaneity (amount of time by which stimulus on the left side must precede or follow the stimulus on the right side for the two stimuli to be perceived as simultaneous), averaged across two response conditions ("which side occurred first" and "which side occurred second")
	Crossed Hands	T1, T2	Visual spatial attention to body (personal) space and near space (in hands working space). Body and near space are incongruent.	
	Board	T1, T2, T3	Visual spatial attention to near space (in hands working space)	
	Wall	T3	Visual spatial attention to near space (on eye level)	
Tactile Temporal Order Judgement	Knees	T3	Tactile spatial attention to body (personal) space	
Greyscales (Nicholls et al., 1999)	Near	T2, T3	Visual spatial attention in near space (on eye level)	Bias index = (Number of responses where the participant chose the stimulus that is darker on the right side as being darker overall – number of responses where the participant chose the stimulus that is darker on the left side as being darker overall) / Total number of responses
	Far	T2	Visual spatial attention in far space (on eye level)	
Mental Number Line Bisection (Sumitani et al., 2014; Zorzi et al., 2002)		T2	Mental representation of space	Mean deviation of subjective midpoint of mental number line from the actual midpoint

Task	Condition	Time points	Measured construct	Operationalization
Global-Local Processing (Bultitude et al., 2009; Navon, 1977)	Global	T2, T3	Processing bias towards global / local information; local interference	Mean reaction times and accuracy rates for congruent and incongruent trials
	Local	T2, T3		

2.3.3.1. Temporal Order Judgment (TOJ)

The TOJ task is a sensitive psychophysical measure of spatial attention (Spence & Parise, 2010). In brief, two identical stimuli are presented, one on each side of the body or external space with different onsets, and participants report their temporal order. We conducted this task in several different conditions across the three sessions, the rationale for which are outlined below.

Visual TOJs in T1 and T2 were conducted in three Presentation conditions (Uncrossed Hands, Crossed Hands, and Board), designed to test if any bias was restricted to the patient's body; extended to near external space; or if it was near space- or body-specific. In the Uncrossed Hands condition, the visual stimuli were presented on the participants' hands (body space), which they placed on the left and right side of their body midline on a table. In that condition, both spatial and body coordinates were available and congruent. In the Crossed Hands condition, the visual stimuli appeared on the participants' hands, which were crossed over their body midline, thus spatial and body coordinates were incongruent (e.g., the left hand was in the right side of space). In the Board condition, the stimuli were presented on the left and right side of a blank board (near / hands working space), thus only spatial coordinates were available. In T3, visual TOJs were conducted in two Presentation conditions to test whether the patient's attention bias is stronger in inferior hands working space (Board), compared to superior near space on eye level (Wall). The Board condition was identical to that described for T2. In the Wall condition, the visual stimuli were projected onto a wall in front of the participants (near space on eye-level). In addition to visual TOJ tasks, we also administered tactile TOJ tasks on the participants' knees in T3 to provide a measure of tactile spatial attention to suprathreshold tactile stimulation in body space that would be more sensitive than the tactile confrontation tests.

The TOJ tasks in the three sessions followed the same general method of constant stimuli. In the visual TOJ tasks, participants were seated at a table with their head stabilised by a chin-rest. Pairs of brief (10ms), identical red point-light stimuli (3mm diameter) were projected 9cm to the left and to the right of the central fixation point on a white background. In the Board condition, the stimuli were projected onto the surface of a 46.5 x 35.5cm board that lay on the table in landscape orientation such that the fixation point was approximately 28cm from the torso. In the Uncrossed / Crossed Hands conditions, the participants placed their hands on top of this board such that the lights projected to the same spatial locations, but were seen on the dorsal surface of the participants' hands (uncrossed, or crossed over the body midline). In the Wall condition (T3), the

fixation point and lights were presented at eye level on a white wall at a 50cm viewing distance. In all visual TOJ tasks, the pairs of lights, one on each side, were presented with different Stimulus Onset Asynchronies (SOAs) in pseudo-random order using custom-built laser pointers that were triggered by Eprime 2.0 software running on Windows 7 operating system (T1 and T2); or via an Arduino platform that was integrated with PsychoPy version 1.85.1 software (Peirce, 2007), running on Windows 10 operating system (T3). In the tactile TOJ tasks, pairs of brief tactile stimuli were delivered as static indentations ("single taps") using miniature electromagnetic solenoid-type stimulators (© Dancer Design) attached to each of participants' knees (centre of kneecaps; 1.8 diameter contact surface) with adhesive rings. The stimulators were controlled via Tactamp amplifier (© Dancer Design) integrated with MATLAB R2013b software (MathWorks Inc., Natick, MA, USA), running on Windows 7 operating system. The participants were seated at the table with their head supported by a chin-rest, eyes closed, and arms hanging loosely next to the torso such that the arms were straight and the fingers pointed to the floor. During each tactile TOJ block, they listened to white noise via headphones to prevent their decisions from being influenced by auditory information. The SOAs were ±5, 15, 30, 60 and 120ms in T1; and ±10, 30, 60, 120, and 240ms for both the visual TOJ tasks in T2 and T3 and the tactile TOJ task in T3. Negative values represent the trials in which the stimulus was presented on the left side first. The SOAs in T2 and T3 were doubled compared to T1 because the patient's responses in the Board condition of T1 suggested that the range of SOAs was insufficient for quantifying her attention bias. Specifically, she indicated that the right light appeared first in 95% of the trials (see Results section). In each session, each SOA was presented 15 times in pseudorandom order, giving 150 trials per block. Each trial began with a pause that varied in length randomly between 500ms and 1000ms. Then the two stimuli were presented with SOAs as detailed above. Following presentation of the two stimuli, participants gave a verbal response to indicate the perceived temporal order of the stimuli. In T1, participants reported "which side occurred first". Given the patient's discomfort with the word "left", it was important to separately account for attentional and response biases (Filbrich et al., 2016; Shore et al., 2001). Hence two Response blocks per Presentation condition were added in T2 and T3, that is, participants reported "which side occurred first" in one block, and "which side occurred second" in another block. They had unlimited time to give their response and were instructed to guess if they were unsure. The researcher keyed the responses into the computer, initiating the next trial. Every block (except for the tactile TOJs) was preceded by a training session with six trials using the maximum SOA to ensure the participants understood the instructions and could perceive the stimuli. If necessary, the training session was repeated until 100% accuracy was achieved. Each block of the task lasted approximately seven minutes.

Overall, there were three visual TOJ blocks in T1 constituting the three Presentation conditions (Board, Uncrossed Hands, Crossed Hands). There were six visual TOJ blocks in T2: 3 Presentation conditions (Board, Uncrossed Hands, Crossed Hands) x 2 Response conditions

("which side occurred first", "which side occurred second"). There were four visual TOJ blocks in T3: 2 Presentation conditions (Board, Wall) x 2 Response conditions; and two tactile TOJ blocks: 1 Presentation condition (Knees) x 2 Response conditions. The order of the blocks was counterbalanced across participants in all sessions.

For every "which side occurred first" block, the proportion of "right occurred first" responses to each SOA was fitted with a cumulative Gaussian using the criterion of maximum likelihood to derive the Point of Subjective Simultaneity (PSS). PSS represents the temporal offset between the two stimuli at which "right" and "left" responses would be equally probable (i.e. at which the psychometric function crosses the proportion of .5). Thus, PSS indicates the amount of time by which the stimulation on the left side should precede (negative PSS) or follow (positive PSS) the stimulation on the right side for the two stimuli to be perceived as simultaneous. For every "which side occurred second" block, the proportion of "left occurred second" responses to each SOA was used to calculate the PSS. By fitting the data in this way, a negative PSS value indicates inattention to the left side, i.e. relative slowing in noticing the stimulation on the left side, regardless of the Response condition. For the primary analysis, the PSS values for each Presentation condition were averaged across the two Response conditions. Additional analyses of the Just Noticeable Difference index, which provides a measure of temporal acuity, are presented in the Supplemental Material.

2.3.3.2. Greyscales

We administered a Greyscales task (Nicholls et al., 1999) to measure visual spatial attention in near and far space. Pairs of identical, vertically aligned, short (9.95° x 1.95°) or long (12.00° x 1.95°) horizontal bars with brightness gradients changing gradually from white to black across their horizontal length were presented simultaneously such that one was the mirror-reverse of the other. One bar was darker on its left side, and the other bar, positioned immediately above or below, was darker on its right side. The bars were on constant display until the participants indicated which bar appeared darker overall. In T2 they gave verbal responses ("top bar was darker" or "bottom bar was darker") that were keyed into the computer by the researcher, and in T3 the participants pressed "up" or "down" arrow keys with their right hand. Following the response, an 18° x 8° random dot pixel mask was displayed for 150ms, and then the next trial began. There were 40 trials per condition, preceded by five demonstration trials. Bias scores were calculated for each participant by subtracting the number of times the participants chose the bar that was darker on the left (the patient's affected) side from the number of times they chose the bar that was darker on the right side, and dividing the difference by the total number of trials. According to this formula, positive score would indicate a bias for making the darkness judgements based on the right side of the stimuli, suggesting inattention to the left side. In T2, the Greyscales task was conducted with the participants standing Near (50cm) and Far (150cm) from the wall-mounted screen. The absolute size of the stimuli was scaled according to the distance,

allowing to use equivalent stimuli to compare these two regions of space within the same task. Such manipulation would not be possible for the visual TOJ set-up using the available equipment. In T3, the Greyscales task was repeated in Near space, with the participants seated at the table with their head stabilised by a chinrest. This was to provide comparative testing conditions to the TOJ tasks from within the same session (T3), and to determine whether the patient's performance on the Greyscales task was stable over time. In all conditions the stimuli were displayed at the participants' eye-level.

2.3.3.3. Mental Number Line Bisection

To measure mental representation of space, a Mental Number Line Bisection task (Sumitani et al., 2014; Zorzi et al., 2002) was used. This task takes advantage of evidence that people implicitly represent numbers in a linear arrangement, with smaller numbers on the left, and larger numbers on the right side of space (Cutini et al., 2014). The participants had to indicate the midpoint numbers between given number intervals (e.g., the midpoint between 11 and 19 is 15), without making any calculations. Our procedure followed those described in previous papers (Rossetti et al., 2004; Zorzi et al., 2002). There were 40 number pairs separated by different intervals (3, 5, 7, and 9) selected from the 1 – 49 number range. The same pairs were presented once in ascending, and once in descending order, giving 80 trials in total. The mean deviation of the perceived midpoint from the actual midpoint between pairs of numbers was calculated. Analogously to the classic line bisection task, positive score would indicate a rightward bias.

2.3.3.5. Global-Local Processing

To test whether the CRPS patient showed neuropsychological deficits typical of right-hemisphere lesions other than inattention to the left side of space, we administered a Global-Local Processing task (Bultitude et al., 2009; Navon, 1977). Participants were asked to identify the global or local levels of hierarchical stimuli (Navon letters; Navon, 1977) presented in the left and right visual fields. The stimuli in T3 were small letters (0.92° x 1.26°) that formed the shape of the same (Congruent) or a different (Incongruent) larger letter (5.13° x 7.10°). Four types of Navon letters (Navon, 1977) were used in each block (two Congruent: small A's forming a large A; small S's forming a large S; and two Incongruent: small A's forming a large S; and small S's forming a large A). The task was conducted in two Target Level conditions over separate blocks: in the Local condition, the participants identified the local level of the stimuli (small letters); in the Global condition, they identified the global level of the stimuli (large letters). The combination of Target level and Stimulus types constituted four conditions: Global Congruent, Global Incongruent, Local Congruent, and Local Incongruent.

Each trial started with a black fixation cross (0.57° x 0.57°) displayed in the centre of a white screen. After 1000ms one of the hierarchical stimuli was presented with its centre located 3.38° to the left (left visual field, LVF) or right (right visual field, RVF) of the fixation cross. The stimulus was presented for 200ms. If the participants identified the local / global stimulus as A,

they pressed the "up" arrow key, and if they identified it as S, they pressed the "down" arrow key. The response keys were aligned with the participant's body midline. Reaction time and accuracy were recorded. Each trial ended with the participant's response without time limit (see Figure 3). Each of the four types of stimuli (two Congruent and two Incongruent) was presented 16 times in each visual field (LVF, RVF) in pseudorandom order, giving 128 trials per Target Level condition. There were 16 training trails before each Target Level condition, with a requirement to achieve at least 75% accuracy level before proceeding to the task.

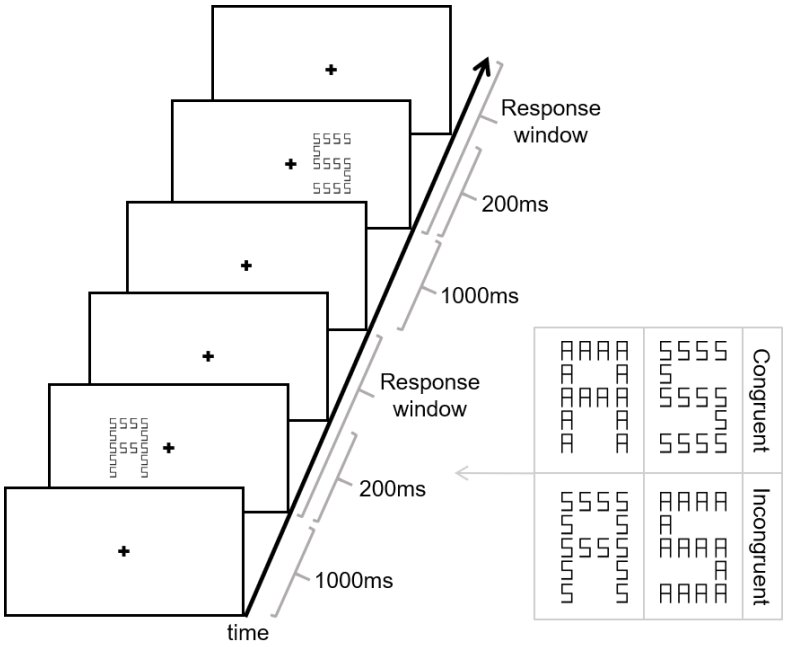

Figure 3. Global-Local Processing task. The time course of two example trials is presented. The right inset panel illustrates four types of stimuli used.

The patient had low accuracy in the Local Incongruent condition in T2 (< 20%) suggesting that she was not able to perform the task as instructed (see Supplemental Material). We inferred that poor peripheral visual acuity could have diminished the patient's ability to perceive the local level (small letters) of the hierarchical stimuli. Therefore, in T3 we measured the patient's peripheral vision, adjusted the size of the visual stimuli (see Supplemental Material), and confirmed that the patient was able to discriminate its local features before administering the main Global-Local Processing task. Thus, only the final procedure of the Global-Local Processing task in T3 is presented in the main text, whereas the procedures used in T2 and to determine the size of the stimuli in T3 can be found in the Supplemental Material.

2.3.4. Visual acuity and peripheral vision

We conducted a set of vision tests, prompted by the patient's self-reported problems with visual acuity and loss of peripheral vision, and her difficulty completing the Global-Local task in T2. The Freiburg visual acuity test (FrACT) was administered in T2 to assess participants' central visual acuity, according to the original procedure (Bach, 1996). The participants were required to

recognise Sloan letters presented in the centre of the screen, in varying size, and at a viewing distance of 50 cm. Participants gave verbal free-choice responses that were keyed into the computer by the researcher. The results were expressed as decimal visual acuity (decVA) and Snellen fraction (normal decVA = 1, equivalent to 20/20 Snellen fraction).

In T3, RareBit Perimetry was used (following the original procedure; Frisén, 2002) to test participants' monocular peripheral vision in both eyes (see Supplemental Material). The participants completed two conditions – one using their left eye, and one using their right eye. The results were expressed in percentages as hit rates in each quadrant of the visual field. The upper and lower quadrants of each visual field were averaged for analysis.

Participants' binocular peripheral visual acuity was also tested in T3. With a key press response, they indicated the orientation (left, right, up, or down) of Landolt C optotypes that were presented at 6 different horizontal distances from a central fixation cross from 3° to 23° eccentricity in both visual fields (12 stimuli per location). The accuracy (%) of responses was calculated for each visual field and position relative to central fixation. Detailed description of the stimuli and procedure is included in Supplemental Material.

2.4. Analyses

The patient's performance was compared to either pre-existing normative data or clinical cut-offs where available; or to data sets from the control participants for each session using Crawford t-tests (Crawford & Howell, 1998) or RSDTs (Crawford & Garthwaite, 2005). These methods enable the comparison of single case data with a control sample while controlling for Type I error rate. The Crawford t-test provides a point estimate of the deviation of the patient's score relative to the control sample mean, equivalent to the *p* value for the significance test. Crawford t-tests were used to compare the patient's scores to those of the controls on the following measures: Bath CRPS Body Perception Disturbance scale, TOJ tasks, Greyscales tasks, Mental Number Line Bisection task, Global-Local Processing tasks, Freiburg visual acuity test, and Landolt C task. The RSDT compares the differences between patient's scores in two different conditions of a task to the distribution of these differences in the control sample data. The RSDTs were performed for the following measures: TOJ tasks (for comparing results for different Presentation conditions and Response conditions), Greyscales task in T2 (Near vs Far), Global-Local Processing tasks (Global vs Local, Global Congruent vs Global Incongruent, and Local Congruent vs Local Incongruent in each Visual Field; LVF vs RVF for global precedence, local interference, and global interference), and RareBit Perimetry (LVF vs RVF). Both Crawford t-test and RSDTs provide point and interval estimates of effect sizes (Crawford et al., 2010). Following the recommendations for reporting statistical results involving comparisons of a single case to controls (Crawford et al., 2010), the raw scores of the patient, and the means and SDs of the

control samples and associated effect sizes are reported. Detailed statistical analysis plans with specified comparisons were pre-registered at osf.io/zx8ad (T2) and osf.io/n6qgv (T3).

3. Results

3.1. Confrontation tests

The results of the confrontation tests for visual and tactile neglect and extinction are presented in Table 4. In line with our hypothesis, when the patient was presented with unilateral visual stimulation in T2, she omitted (failed to detect) twice as many stimuli on her left (affected) side than on the right, suggesting neglect of the left side. However, she omitted no (left or right) unilateral stimuli in T3. Omissions of some left-sided visual stimuli during bilateral presentation in T2 and T3 are indicative of extinction. In T3, there were also signs of extinction of right-sided visual stimuli. A pattern of neglect and extinction similar to that in visual tests was also found for tactile stimulation in T2, however, there were only signs of tactile extinction on the left side in T3. The patient also reported some referred sensations (unilateral touch was concurrently perceived bilaterally) and allochiria (unilateral stimulation to the left side was only perceived on the right side of the body). There were no other visual or tactile false detections. Contrary to our predictions, the patient showed no signs of motor neglect or motor extinction when they were assessed in T2.

Table 4 *Percentage of omissions, referred sensations, and allochiria on the confrontation tests*

Time point	Left extinction	Left neglect	Right extinction	Right neglect	Referred	Allochiria
Visual						
T1	17%	50%	0%	0%	0%	0%
T2	40%	80%	0%	40%	0%	0%
T3	40%	0%	20%	0%	10%	0%
Tactile (knees) eyes closed						
T2	40%	20%	0%	0%	10%	10%
T3	60%	0%	0%	0%	20%	0%
Tactile (knees) eyes open						
T2	80%	20%	0%	0%	10%	10%

Note. T1, = Session 1; T2 = Session 2; T3 = Session 3. In T1 the experimenter presented 6 left, 5 right, and 6 bilateral stimuli. In T2 and T3 the experimenter presented 5 right, 5 left, and 5 bilateral stimuli in a pre-defined pseudorandom order for all tests.

3.2. Neuropsychological tests

As presented in Table 5, no systematic lateralised attention bias was found on standard neuropsychological assessments of neglect in T2.

Table 5 *The patient's scores on the subtests the Behavioural Inattention Test battery and other "bedside" tests of neglect administered in T2*

Measure (region tested)	Patient's scores	Cut-off scores
Behavioural Inattention Test battery – conventional (near space)	144	< 129
Line crossing	0%	> 70% omissions
Letter cancellation	2	> 4 omissions
Star cancellation	0.5	< 0.46 or > 0.54 side-to-side ratio
Figure copying	0	Any major lateral omissions or distortions
Shape copying	0	
Line bisection	5.6% left, 0.2% left, 5.1% right	> 14% deviation from the centre
Man, clock, and butterfly drawing	0	Any lateral omissions or distortions
Behavioural Inattention Test battery – behavioural: Article reading (near space)	< 1%	> 42% omitted words
Bells cancellation (near space)	1	Side-to-side difference of 3 omissions
Fluff test (body space)		
Left side	14 (eyes closed); 15 (eyes open)	< 13 detached targets
Right side	7 (eyes closed); 9 (eyes open)	< 9 detached targets
Room description (far space)		
Left side	2	> 2 omitted items
Right side	2	> 2 omitted items

3.3. Experimental measures of attention

3.3.1. Temporal Order Judgements

For the Crossed Hands condition of the visual TOJ tasks (T1 and T2), the lack of systematic pattern of the patient's responses across different temporal offsets prevented fitting the cumulative Gaussian to determine the PSS. Thus, the hypotheses regarding the Crossed Hands condition could not be addressed and no results are presented for this. In T1, the patient responded "right" on 95% of trials (to the question "which side occurred first?") in the Uncrossed Hands condition and thus there was insufficient variability in the responses to fit the cumulative Gaussian and determine the PSS. For this condition, the patient's visual attention bias was conservatively estimated using nearest neighbour replacement with the PSS value of the patient with the most extreme fittable data in the same group study (Bultitude et al., 2017). Her pattern of responses suggests marked inattention to the left side of her body, but could also be attributed to response bias, which was not controlled for in T1. The cumulative Gaussian was successfully fitted for all

the remaining TOJ tasks administered across the three research sessions, indicating that the patient and control participants were able to complete these tasks as instructed.

The analyses confirmed a significant response bias, that is, differences between Response conditions ("which side occurred first?" and "which side occurred second?") on visual TOJs in hands working space in T2, $t(11) = 2.64$, $p = .011$, $z_{cc} = -2.939$, 95% CI [-4.502, -1.617], and on tactile TOJs in T3, $t(11) = 2.54$, $p = .027$, $z_{cc} = -2.802$, 95% CI [-5.217, -0.841]. The direction of the differences between PSS values from the two Response conditions (Table S1 in Supplemental Material) suggests that the patient was less likely to give "left" responses regardless of the Response condition. No significant response bias was found in other TOJ task conditions in T2 and T3. The patient's and controls' mean PSS values in each Response condition, and PSS values averaged across two Response conditions in each Presentation condition, are reported in Supplemental Material (Table S1). The effects of response bias on all attained responses in T2 and T3 were removed through averaging PSS values across two Response conditions. The PSS results are illustrated in Figure 4.

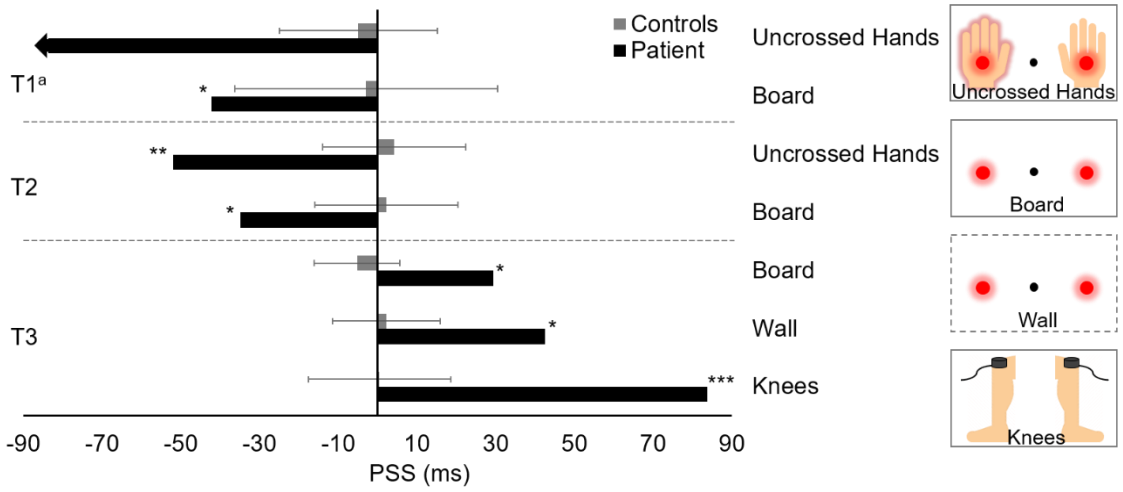

Figure 4. Temporal Order Judgement task (TOJ) - Point of Subjective Simultaneity (PSS). The patient's and controls' mean PSS values for each Presentation condition (right inset panel) across the three sessions. T2 and T3 data are averaged over Response conditions ("which side occurred first?" and "which side occurred second?"; see Table S1 in Supplemental Material for un-averaged data) to control for response bias. A negative PSS value indicates inattention to the left (affected) side. Thus, negative PSS values for the patient's visual TOJs in T1 and T2 relative to controls' are consistent with inattention to the left (affected) side of the body and near space. Positive PSS values for the patient relative to controls' in T3 are consistent with hyperattention to the left side of her body (tactile stimulation) and near space on eye level and hands working space (visual stimulation). Error bars represent standard deviations of the controls' mean PSSs and are not presented for the patient's single PSS values. Due to "right" response on 95% of trials in the Uncrossed Hands condition in T1, nearest neighbour replacement was used to conservatively estimate the patient's PSS from other patient responses, and an arrow indicates that the bias could be more extreme. *$p < .05$; **$p < .01$; ***$p < .001$. T1 = Session 1; T2 = Session 2; T3 = Session 3. [a] The TOJ tasks in T1 were conducted using a smaller range of stimulus

onset asynchronies compared to T2 and T3, and without controlling for response bias (see Materials and Methods section for further details).

In T2, we used a larger range of SOAs than in T1 to increase the likelihood of being able to quantify the patient's attention bias, and controlled for response bias. The results for the Uncrossed hands condition in T2 were broadly consistent with inattention to the left side in T1, and were significantly different to controls' mean score, $t(11) = -2.96$, $p = .006$, $z_{cc} = -3.083$, 95% CI [-4.463, -1.682]. The patient showed significant inattention to the left side of hands working space (Board) in T1 and T2 compared to controls, $t(11) = -2.00$, $p = .038$, $z_{cc} = -2.045$, 95% CI [-3.048, -1.017], but hyperattention to that side in T3, $t(11) = 3.04$, $p = .011$, $z_{cc} = 3.160$, 95% CI [1.730, 4.568], demonstrating a reversal in the direction of the spatial attention bias between T2 and T3. In T3, the patient also showed significant hyperattention to the left side of near space on eye level (Wall), $t(11) = 2.83$, $p = .016$, $z_{cc} = 2.943$, 95% CI [1.594, 4.270], and hyperattention to touch delivered to the knees on the left side of the body, $t(11) = 4.41$, $p = .001$, $z_{cc} = 4.594$, 95% CI [2.613, 6.561]. In summary, the patient's PSS scores were significantly different to control participants in all TOJ conditions across all sessions. We found inattention to the affected side in all tested conditions in T1 and T2 and hyperattention to the affected side in all tested conditions in T3. These attention biases were present even when response bias was controlled for in T2 and T3.

Contrary to our hypotheses, the magnitude of the patient's visual spatial attention bias was not larger in body space (Uncrossed Hands) compared to hands working space (Board) in T2, $t(11) = 0.94$, $p = .188$, $z_{cc} = 1.058$, 95% CI [-0.361, 2.618]. There was also no significant difference in the magnitude of attention bias between hands working space (Board) and near space on eye level (Wall) in T3, $t(11) = 0.17$, $p = .435$, $z_{cc} = 0.186$, 95% CI [-1.363, 1.756]. Thus, within these sessions, the *magnitude* of the attention bias shown by the patient was similar regardless of which modality / spatial domain was tested, although the *direction* of attention bias for T3 was different to T1 and T2.

3.3.2. Greyscales

Counter to our hypotheses, the patient's attention bias scores in the Near condition of the Greyscales task (T2 = -0.30; T3 = -0.45) were not significantly different from the mean (±*SD*) scores of the healthy controls (T2 = -0.23±0.41; T3 = -0.06±0.39), neither in T2, $t(11) = -0.18$, $p = .432$, $z_{cc} = -0.182$, 95% CI [-0.749, 0.393], nor in T3, $t(11) = -0.96$, $p = .360$, $z_{cc} = -0.995$, 95% CI [-1.679, 0.281]. This was also the case for the Far condition of the Greyscales task (patient T2 = -0.40; controls T2 = -0.25±0.36), $t(11) = -0.39$, $p = .350$, $z_{cc} = -0.41$, 95% CI [-0.993, 0.189]. The difference between bias scores for Near vs Far condition for the patient was not significantly different from that for the controls in T2, $t(11) = 0.26$, $p = .801$, $z_{cc} = 0.291$, 95% CI [-0.302, 0.898].

3.3.3. Mental Number Line Bisection

Contrary to what we predicted, the patient did not demonstrate spatial bias in the bisections of mental number line (bias score = 0.13) compared to healthy controls (mean bias score = 0.10±0.09), $t(11) = 0.31$, $p = .764$, $z_{cc} = 0.321$, 95% CI [-0.268, 0.894].

3.3.4. Global-Local Processing

Since the patient's results from T2 suggest the stimuli were too small for her to be able to perform the task as instructed (see Supplemental Material), only the results from T3 are reported in the main text. The patient's accuracy rates for incongruent trials in the Global and Local conditions in T3 were ≤ 50% (Figure 5). Thus, only 15/32 LVF trials, and 14/32 RVF trials were included in the reaction time analyses for these conditions (Figure 6).

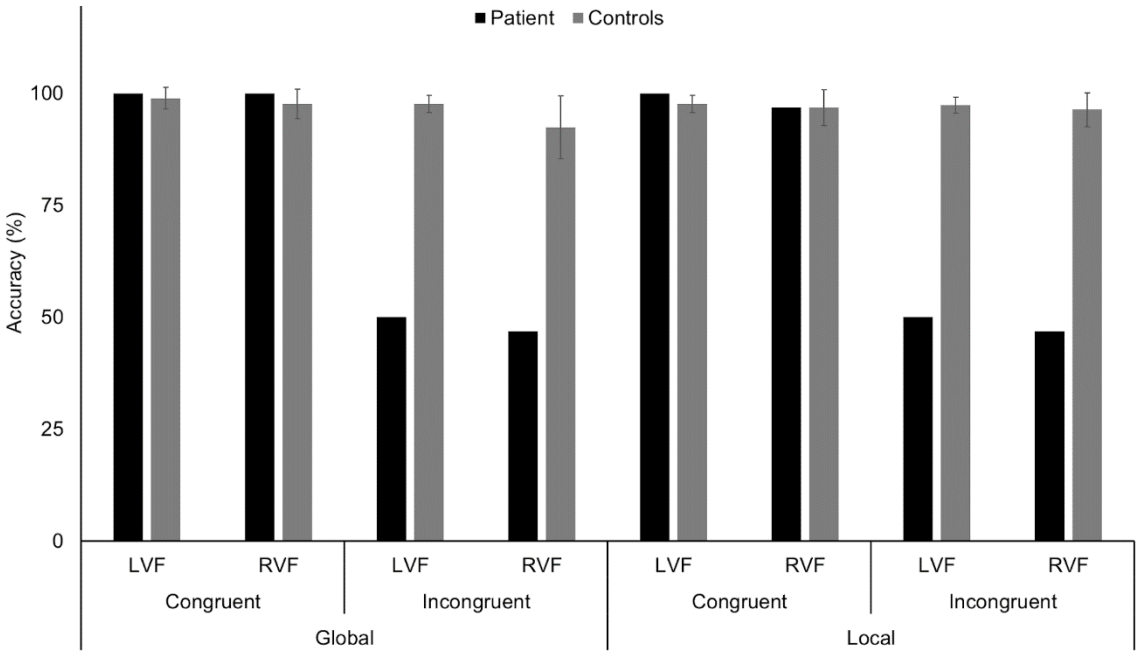

Figure 5. Global-Local Processing task (T3) – accuracy. The patient's and controls' mean accuracy rates (%) for congruent and incongruent stimuli in left and right visual field (LVF and RVF, respectively) in T3. Error bars represent standard deviations of the controls' means and are not presented for the patient's single accuracy rates.

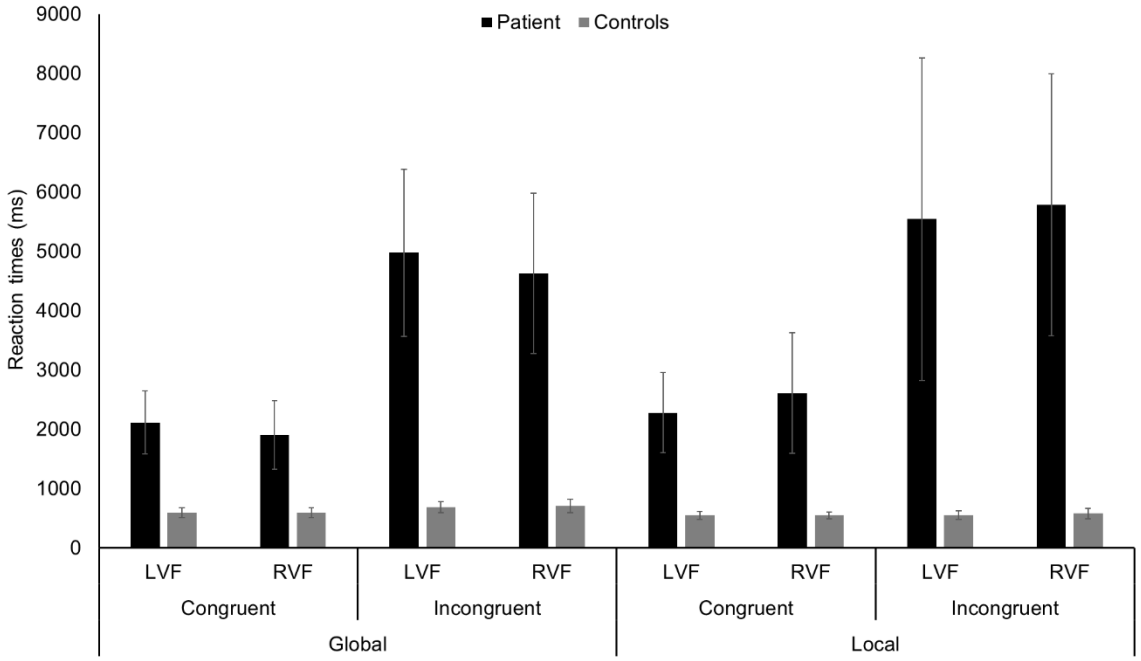

Figure 6. Global-Local Processing task (T3) – reaction times. The patient's and controls' mean reaction times (ms) for congruent and incongruent stimuli in left and right visual field (LVF and RVF, respectively) in T3. Error bars represent between-subjects standard deviations of the controls' means and within-subject standard deviations for the patient.

To test whether the patient showed a local processing bias, we first compared her performance in Global Congruent vs Local Congruent conditions to the control sample performance in these conditions. Contrary to our predictions, the patient's reactions times were significantly faster for the Global vs Local levels compared to controls in the LVF, $t(11) = 9.94$, $p < .001$, $z_{cc} = -14.291$, 95% CI [-28.550, -1.198] and the RVF, $t(11) = 20.19$, $p < .001$, $z_{cc} = -43.099$, 95% CI [-68.051, -21.745]. The differences in the patient's accuracy rates for Global vs Local levels compared to controls were not significant in either visual field (ps > .05).

Expecting that the patient would show greater interference from irrelevant local level information, we used RSDTs to determine if the difference in performance for Global Congruent vs Global Incongruent conditions was higher for the patient compared to the controls. The patient had larger local interference relative to the controls, both in accuracy rates for the LVF, $t(11) = 13.61$, $p < .001$, $z_{cc} = 14.447$, 95% CI [9.100, 25.624], and the RVF, $t(11) = 7.34$, $p < .001$, $z_{cc} = 9.344$, 95% CI [5.565, 13.961], and reaction times in the LVF, $t(11) = 27.38$, $p < .001$, $z_{cc} = -75.574$, 95% CI [-114.677, -42.652], and the RVF, $t(11) = 17.81$, $p < .001$, $z_{cc} = -34.616$, 95% CI [-56.115, -16.074]. This suggests that, in line with our hypothesis, the patient was significantly less accurate and slower in Global Incongruent than Global Congruent trials relative to controls.

To evaluate whether the patient would show smaller interference from irrelevant global level information (consistent with a local processing bias), we used RSDTs to determine if the difference in performance for Local Congruent vs Local Incongruent conditions was lower for the patient compared to the controls. Contrary to this prediction, the patient showed higher global

interference compared to controls. This is evidenced by significant results of RSDTs for accuracy rates in the LVF, $t(11) = 15.26$, $p < .001$, $z_{cc} = 20.878$, 95% CI [11.741, 32.300], and the RVF, $t(11) = 9.90$, $p < .001$, $z_{cc} = 13.005$, 95% CI [7.329, 20.013], and reaction times in the LVF, $t(11) = 33.19$, $p < .001$, $z_{cc} = -106.477$, 95% CI [-162.723, -59.128], and the RVF, $t(11) = 25.38$, $p < .001$, $z_{cc} = -65.559$, 95% CI [-107.019, -29.188]. That is, the patient was less accurate and slower in Local Incongruent than Local Congruent trials, and these differences were larger than in the control sample.

Finally, we derived the local / global interference ratios from the reaction time data. The patient's ratios were 0.88 (LVF) and 0.86 (RVF), consistent with a global processing bias (greater global than local interference) and contradicting our predictions. However, this was not significantly different to the ratios of the controls (LVF = -1.97; RVF = -0.46). Overall, the patient showed larger local *and* global interference than controls in both visual fields. Statistical comparisons between LVF and RVF are reported in the Supplemental Material.

3.4. Visual acuity and peripheral vision

The results of the FrACT and the Rarebit perimetry tests showed that the patient had significantly impaired monocular and binocular visual acuity compared to the control groups (Table 6). Perimetry also showed that in both eyes, the patient had significantly greater asymmetry between her LVF and RVF acuity compared to controls, with better peripheral vision in the left (affected) visual field.

Table 6 *The patient's results for visual acuity test in T2 and perimetry in T3 compared to healthy controls*

				Significance test			**Estimated effect size**	
Measure	**Time point**	**Patient's score**	**Control sample score (*M*±*SD*)**	***t***	***df***	***p***	z_{cc}	**95% CI**
FrACT (decVA; Snellen fraction)[1]	T2	.38; 20/50	.52±.03; 20/40	-3.89[a]	11	.003	-4.046	-5.797, -2.279
RareBit Perimetry (hit rate, %)								
Left eye	T3			3.88[b]	8[2]	.005	-4.928	-10.867, 0.360
LVF		46.85	93.72±5.01					
RVF		44.17	95.74±8.29					
Right eye	T3			6.05[b]	8[2]	<.001	-8.473	-16.593, -1.358
LVF		45.00	96.20±4.25					
RVF		42.84	93.28±6.81					

Note. FrACT = Freiburg visual acuity test; LVF = left visual field; RVF = right visual field. [1] Normal decimal visual acuity (decVA) equals 1 (equivalent of 20/20 Snellen fraction), with lower scores indicating impaired visual acuity. [2] Due to results saving error, only 9 out of 12 complete data sets from control participants were obtained for this test. [a] Crawford t test. [b] Revised Standardised Difference Test.

Figure 7 illustrates the percentage accuracy of the patient's and controls' responses on the test of binocular peripheral vision over different eccentricities, as tested in T3. The patient had worse than normal performance for eccentricities of 12º or greater, and there was little difference between her performance for the LVF and RVF.

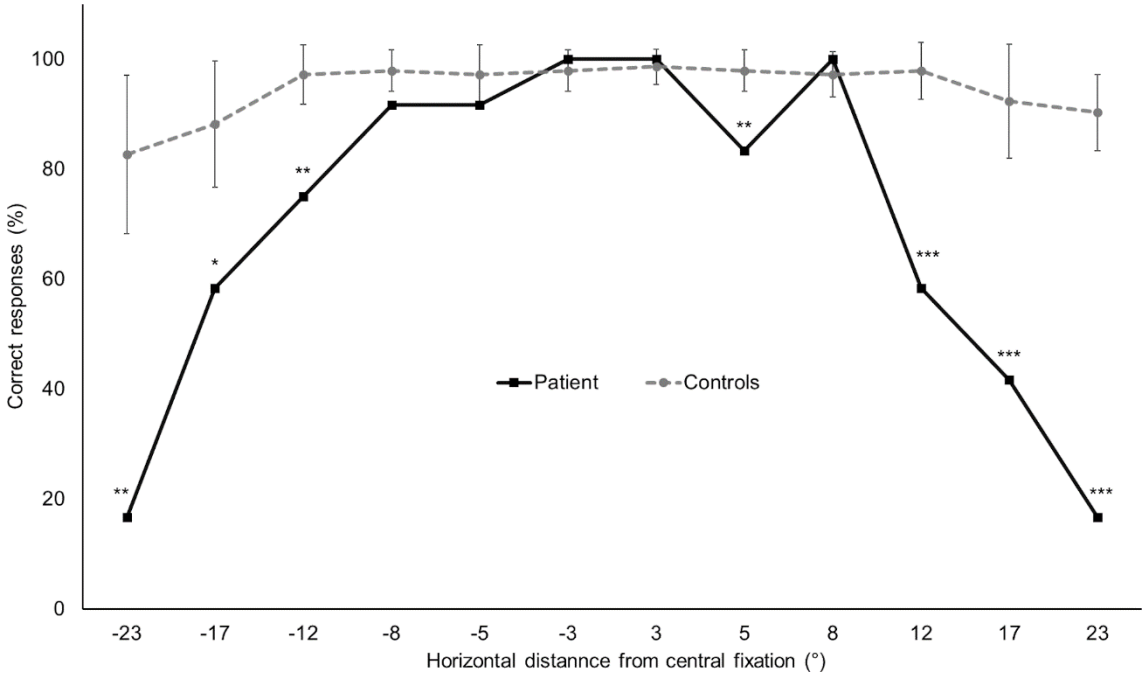

Figure 7. Landolt C test. The patient's and controls' mean accuracy rates for different positions of Landolt C optotypes, showing that the patient had impaired visual acuity in more peripheral locations. Negative distance indicates positions in the left (affected) visual field. Error bars represent standard deviation of the controls' means. *$p < .05$; **$p < .01$; ***$p < .001$.

4. Discussion

We examined spatial attention changes in a woman with CRPS affecting her left arm, who has previously presented with pronounced attention bias, yet she had no known brain pathology and scored within the normal range on general cognitive assessments. In the current study, she showed neglect and extinction of visual and tactile stimulation on her affected side on confrontation tests, but no motor neglect. Based on her severe attention bias in T1, we hypothesised that the patient would show attention bias on classic "bedside" tests when tested in T2. However, her performance was normal, consistent with previous studies (Christophe, Chabanat, et al., 2016; Förderreuther et al., 2004; Kolb et al., 2012; Reid et al., 2016) and the conclusion that any attention bias shown by people with CRPS is likely to be subtle and only detected using sensitive tasks (Bultitude et al., 2017; Filbrich et al., 2017; Moseley et al., 2009, 2012; Reid et al., 2016). Also in keeping with this conclusion, her visual and tactile attention was biased on TOJ tasks that

required judging the order of pairs of visual and tactile stimuli that were presented in body and / or near space. These attention biases were present even when we controlled for response bias. They cannot be explained by hemisensory impairment because the patient's peripheral vision, although impaired overall, was better in the affected hemifield, and her tactile sensitivity was equal on both lower limbs (where we tested tactile spatial attention). Contrary to our hypotheses, the attention biases were not stronger in body space compared to near space, or in near hands working space compared to near space on eye level. No evidence of attention bias in near, far, or imagined space was found on two other experimental measures of spatial cognition (the Greyscales task and Mental Number Line Bisection). Although there was no specific local processing bias, often associated with right hemisphere dysfunction (Bultitude et al., 2009; Navon, 1977), the patient had non-lateralised cognitive difficulties in processing incongruent hierarchical visual information. These were evidenced by larger than normal global and local interference effects in the Global-Local task.

The most striking result of our study is that the CRPS patient presented with a dramatic change in TOJs from inattention to the affected side in T1 and T2, to hyperattention in T3, despite no change in pain or body representation distortion. The direction of the bias (inattention or hyperattention to the affected side) was consistent across the different conditions of the TOJ task *within* each session, and only the direction of bias changed *between* the second and third session. However, it should be noted that only one presentation condition (visual stimuli appearing on a blank board in near space) was consistent across all three sessions. No previous study has investigated whether spatial attention bias in CRPS is stable over time, and there are only a handful of cases of brain-lesioned patients showing opposite directions of attention bias (on different assessments: Beschin, Basso, & Sala, 2000; Costello & Warrington, 1987; Dove, Eskes, Klein, & Shore, 2007; Van der Stoep et al., 2013; or over time: Kim et al., 1999; Kwon & Heilman, 1991). To the best of our knowledge, the only study that involves repeated testing of spatial cognition in CRPS patients was that of Christophe, Chabanat, et al. (2016), who did not find any deficits in spatial attention in seven patients with CRPS, neither before nor after they underwent treatment that resulted in pain reduction. Together with these results, our findings suggest that the direction of attention bias can be independent of pain and body representation distortion. Moreover, the direction of attention bias may not be stable over time, despite sustained pathology.

4.1. Attention in body space and near space

Post-stroke neglect can manifest in one or multiple sensory modalities (Barbieri & De Renzi, 1989; Bisiach et al., 2004; Cubelli et al., 1991; Kerkhoff, 2001; Marsh & Hillis, 2008; Vallar, 1998). Although most previous studies on CRPS investigated one modality at a time (Bultitude et al., 2017; Moseley et al., 2009), there is also evidence that attention bias can dissociate, being evident only for visual, but not tactile information (Filbrich et al., 2017). In this study, the CRPS

patient's attention bias on confrontation tests and TOJ tasks generalised across visual and tactile modalities. No signs of motor neglect were found, consistent with the evidence of dissociations between perceptual and motor neglect as has been shown in post-stroke patients (Bisiach et al., 1990; Buxbaum et al., 2004; Liu et al., 1992), although it is possible that motor neglect would become evident if a more sensitive test was used (Reid et al., 2018).

It has been proposed that spatial cognition deficits in CRPS are driven by distorted body perception ("somatospatial inattention" hypothesis; Bultitude et al., 2017; Reid et al., 2016) and / or limited amount of action in the affected side of space (Punt et al., 2013). The patient in the current study showed severe distortions in body representation. These were evidenced by high BPDS scores, the patient's own descriptions of her affected hand (see Figure 1), her aversion to the words "wrist" and "left", preference for keeping her arm out of sight (reminiscent of misoplegia; Bartolomeo et al., 2017; Critchley, 1974; Lewis et al., 2007), and the evidence of a significant response bias in some TOJ tasks. She also reported high pain-related fear of movement. If such specific relationships existed between body representation, action in near space, and attention bias, the patient's bias should be greater in body space compared to near space, and in hands working space (where the arms are more frequently positioned and moved) compared to near space on eye level.

Partly in line with our predictions, the patient showed significant attention biases in body space and near hands working space in T1 and T2 in TOJ tasks. However, the bias was not significantly stronger when the TOJs involved the patient's hands compared to other conditions, nor for hands working space compared to near space on eye level in T3. The patient also presented with biased attention to tactile stimuli on her left side of the body when the stimulation was delivered to her lower limbs, which were unaffected by CRPS. Finally, the direction of her attention bias changed from inattention to hyperattention to the affected side, while pain intensity, body representation, and fear of movement remained the same between sessions. This suggests that there might not be a direct association between pain intensity, severity of body representation distortion, and direction of spatial attention bias. These findings are not fully consistent with the "somatospatial inattention" hypothesis suggesting that the relationship between spatial attention and body representation is also interrelated with pain in CRPS (Moseley et al., 2012; Reid et al., 2016), the idea of action-driven inattention (Punt et al., 2013), or our predictions regarding the magnitude of bias in different regions of space. Nonetheless, current results corroborate our previous conclusion that visual attention bias can be present both when the body related information is involved in the task, and when it is not relevant (Bultitude et al., 2017).

Attention biases can be generalised or specific to certain regions of space. Post-stroke neglect can arise for the external space within (near) and beyond (far) the patients' reach (Kerkhoff, 2001; Pizzamiglio et al., 1989). Considering previous evidence of mislocating visual stimuli in far space relative to one's body in the opposite direction to the spatial bias often found in near space in

CRPS (Christophe, Chabanat, et al., 2016; Jacquin-Courtois et al., 2017; Sumitani, Rossetti, et al., 2007; Sumitani et al., 2014; Uematsu et al., 2009), we predicted that the patient's attention bias in far space would be absent or opposite to the bias in near space. She reported previous problems with veering off to the left while walking, which could suggest difficulties with integrating the sense of the position and orientation of her whole body with external visual information. When the patient's attention in far space was formally tested using the Greyscales task, she showed no attention bias (consistent with our prediction). However, contrary to our prediction, she also showed no bias when tested on the same task in near space, despite evidence of attention biases on TOJ tasks in near space. This difference in the results could be because the participants performed the Greyscales task under free viewing conditions, thus employing overt attention, whereas TOJs of brief stimuli employ covert attention (Wright & Ward, 2008). The same explanation would apply to the discrepancy between normal performance on "bedside" tests of neglect, and evidence of neglect and / or extinction on confrontation tests. In our study, the attention bias appeared to be present only when the patient had to quickly, covertly attend to visual or tactile information, but not when she had the opportunity to explore the visual display freely over longer periods. Further research to examine attention in far space could use a TOJ task, which was not possible using the available equipment in the current study.

One possible limitation to interpreting the results of the visual tasks is the patient's impaired visual acuity and loss of peripheral vision, combined with her complaints about double vision. We must consider that the patient's visual deficits could have contributed to her impaired performance on visual confrontation tests, TOJs, and Global-Local Processing task, despite her using corrective glasses during each session. Indeed, our interpretation of the results from the Global-Local Processing task administered in T2 was that the patient was unable to discern the local level of the Navon stimuli (see Supplemental Material). However, the patient's performance on the same task in T3 cannot be attributed to her visual acuity impairments because in this session we systematically increased the size of the Global-Local stimuli until the patient could consistently discriminate their local features before we proceeded with the main Global-Local Processing task, and she had similar accuracy for identifying the Local and Global levels of the stimuli. The patient showed deficits in her peripheral visual acuity as measured in T3. This was slightly worse in the right visual hemifield for monocular vision, but approximately the same for the left and right visual fields when tested binocularly. This primary visual deficit cannot explain the biases away from her affected side that she showed in confrontation testing and previous TOJ tasks. It might have contributed to the bias towards her affected side on the visual TOJ tasks in T3, although it appears unlikely that such a small difference in peripheral vision in the left and right visual fields could completely explain the bias on the TOJ task. Co-morbid eye diseases and conditions have been scarcely reported in CRPS literature, despite their prevalence in clinical anecdotes (Hall et al., 2011). Viewing ambiguous images has been found to exacerbate pain and other CRPS symptoms (Hall et al., 2011), including asymmetric vasomotor response (Cohen et

al., 2012), possibly through supraspinal interactions between pain networks and somatomotor and autonomic pathways. These previous and present findings advocate an idea that centrally modulated visual symptoms might be associated with pain and other diagnostic signs of CRPS. The aetiology of the patient's visual impairment is unknown and based on the available data it is not possible to differentiate between central and peripheral mechanisms; yet the similar patterns in both eyes and visual fields suggest that central mechanisms cannot be ruled out.

We considered the possibility that the patient's peripheral vision loss could account for the lack of evidence of spatial attention bias in the Greyscales tasks. The most discriminating parts of the greyscale stimuli are their edges, thus if the patient made her judgements based on the central parts of the stimuli alone then she would be less likely to show a bias. However, this is unlikely because the entirety of the images was presented within the range of the patient's visual field that was not significantly impaired relative to controls (see Figure 7), and this task was performed under free-viewing conditions.

In contrast to previous findings in patients with CRPS (Christophe, Delporte, et al., 2016; Jacquin-Courtois et al., 2017; Sumitani et al., 2014) and post-stroke neglect (Priftis et al., 2006; Rossetti et al., 2004; Zorzi et al., 2002, 2006), there was no evidence of a bias in the mental representation of space assessed using Mental Number Line Bisection. Overall, the CPRS patient presented with spatial attention biases only in body and near space (as often found in neglect; Buxbaum et al., 2004; Committeri et al., 2007), while far and imagined space were not affected by spatial deficits. Similar dissociations in attention bias in different regions of space and / or across different tasks have been demonstrated in neglect following a stroke, which can manifest in near, but not far space (Aimola et al., 2012; Halligan & Marshall, 1991; Keller et al., 2005).

4.2. Implications of reversal of the attention bias

We propose two speculative explanations of the "reversal" of attention bias observed between sessions. First, people with CRPS can be hypervigilant to potential spreading of CRPS symptoms to other limbs (Rijn et al., 2011), thus any new pain might lead to increased monitoring of sensations and other information on the affected parts of the body. The patient injured her left leg five months prior to the third session of this study, and at that time reported discontinuous pain and other symptoms. These could have attracted her attention back to the left side, after years of neglecting her CRPS-affected arm. One possible mechanism of such a change is that new pain ipsilateral to the patient's affected arm could have increased the level of arousal that facilitated orienting of attention towards the CRPS-affected side. For instance, people who had a right hemisphere stroke often present with a non-spatial deficit of alertness, and phasic alerting of attention has been found to improve their perception of usually "neglected" contralesional stimuli (Robertson, Mattingley, Rorden, & Driver, 1998). Alternatively, our patient's attention towards the affected side could have been directly driven by increased somatosensory input from that side

of the body due to new pain in the lower limb (Sumitani, Shibata, et al., 2007). Hyperattention to the affected side could also be considered a strategy to cope with this exaggerated input and avoid further escalation of pain. For instance, Christophe, Delporte, et al. (2016) and Jacquin-Courtois et al. (2017) attributed the hyperattention of their CRPS patient to avoidance of external (hyperalgesia, allodynia) or movement induced painful stimulation (kinesiophobia), as protective attention bias towards the affected side. Such an interpretation, however, could not explain the hyperattention shown by our patient in the third session, since her kinesiophobia was comparable in all three sessions, including T1 and T2 in which she showed inattention to the affected side.

The second possible explanation is that by T3 the patient might have been undergoing adaptive reengagement with the affected limb, thanks to comprehensive pain management programmes she attended throughout the entire three-year period of this study. These are focused on CRPS rehabilitation, including physiotherapy, hydrotherapy, occupational therapy, and psychological support. During the sessions, patients are encouraged to actively focus on their affected limb and move it, they work towards reconditioning normal movement (as compared to compensatory movements), learn strategies aimed at restoring the normal level of daily function (including work, personal care, leisure activities), coping with emotional disturbances, and self-managing CRPS in long-term. Thus, the "reversal" of attention bias could have been an effect of increasing attention and functional use of the affected limb during the inpatient programme that the patient completed between T2 and T3. During the months following the final research session we learned that, for the first time since her injury, the patient had begun to take part in leisure and sporting activities that involved her affected arm and whole body, despite having experienced no reduction in pain and other CRPS symptoms. That is, the patient underwent psychological and behavioural change. A limitation of this study is that no data on the patient's emotional state was collected during T2 and T3, as mood could potentially exert effects on attention (Tucker et al., 1999).

Paradoxically, although the patient's TOJ responses in T3 indicated hyperattention to her affected side, confrontation testing revealed visual and tactile extinction of the affected side in the same session. Yet the pattern of changes in the patient's performance on visual confrontation tests is more complex and demonstrates amelioration of left neglect in T3 compared to previous sessions, and emergence of right extinction in T3, which was not present in the previous sessions. This trend to some extent appears to follow the changes over time observed on the TOJ tasks, although extinction of the left stimuli in T3 was still twice as frequent as for the right stimuli. In line with the patient's behavioural change one could speculate a development of compensatory strategy to endogenously orient attention towards the affected side (Dove et al., 2007), which was effective on TOJs in T3, but less so on confrontation tests, potentially due to chronicity of her inattention or task specificity. Similarly, patients who had a stroke can develop ipsilesional neglect over time, which is thought to arise due to compensatory left-sided scanning strategies and non-lateralised attention deficits (Robertson et al., 1994; Williamson et al., 2018). The design of the current study,

which was not intended to examine changes in the direction of attention bias over time, is limited in that only the visual confrontation tests and the Board condition of the TOJ task were consistent across all testing sessions. It could be informative to investigate whether the patient's reversed attention bias persisted or generalized across other measures over longer time periods; however, it was not feasible to arrange another follow-up session.

Our conclusion that the attention bias reversed over time has implications for treatments that attempt to reduce CRPS pain through addressing this bias, such as prism adaptation. Prism adaptation is a sensory-motor rehabilitation method that is commonly used to reduce spatial attention deficits in post-stroke neglect patients (Rossetti et al., 1998). There is evidence of pain reduction following prism adaptation in a total of 13 CRPS patients across three independent studies (Bultitude & Rafal, 2010; Christophe, Chabanat, et al., 2016; Sumitani, Rossetti, et al., 2007). Although the mechanism of prism adaptation treatment of CRPS is as yet unclear, pain reduction is thought to rely on increasing attention to the CRPS-affected side. For example, when a CRPS patient underwent prism adaptation to induce an attention shift away from the affected side, her pain increased (Sumitani, Rossetti, et al., 2007). If the direction of prismatic shift relative to the attention bias of the patient is an important mechanism for treatment, then the variability in attention bias demonstrated in the current case study has ramifications for how to implement prism adaptation for CRPS. For example, patients presenting with hyperattention to their affected side may respond to the treatment differently to those presenting with inattention.

Nonetheless, in our patient the direction of attention bias appears to be independent of pain intensity. Despite substantial evidence suggesting that unilateral chronic pain such as CRPS affects the perception of body and near space in the form of inattention to the affected side (Bultitude et al., 2017; Filbrich et al., 2017; Moseley et al., 2009, 2012; Reid et al., 2016), the present finding gives rise to a question of whether these two outcomes (pain and inattention) are dependent upon each other in CRPS. In conjunction with the evidence of the beneficial effects of prism adaptation on pain in patients without apparent deficits in spatial cognition (Christophe, Chabanat, et al., 2016), and reports of pain intensity being unrelated to spatial attention bias (Bultitude et al., 2017; Reinersmann et al., 2012), it appears that the emergence of these biases in CRPS does not simply depend on sensory information from the affected limb (or vice versa). This suggests that prism adaptation reduces pain through some mechanism(s) other than by increasing attention to the affected limb. Alternatively, since none of the published studies on prism adaptation in CRPS used control treatment conditions, it is possible that its previously reported effects on pain are due to a placebo response.

4.3. Cortical underpinnings of neuropsychological symptoms in CRPS

Although in CRPS the symptoms of attention bias can occur without any brain damage, they could be related to the disruption of the same attentional networks that give rise to post-stroke neglect.

The posterior parietal cortex (PPC; in particular the supramarginal gyrus at the temporal-parietal junction) has been implicated as a crucial lesion site for neglect (Halligan, Fink, Marshall, & Vallar, 2003). The PPC is involved in spatial processing such as orienting of attention and target detection, and constructing spatial representations of the body and external space (Carter et al., 2017; Corbetta & Shulman, 2002; Grefkes & Fink, 2005; Posner et al., 1984; Vallar et al., 1999). Neglect in body space has been linked to lesions of the supramarginal gyrus (important for egocentric representation of our body in space; Committeri et al., 2007; Galati, Committeri, Sanes, & Pizzamiglio, 2001) and to functional disconnection between parietal regions involved in integrating proprioceptive and somatosensory information (Committeri et al., 2007; Coslett, 1998). In contrast, neglect in near space has been associated with lesions to fronto-temporal regions that form part of the ventral circuit for exogenous allocation and reorienting of attention in space (Committeri et al., 2007; Corbetta & Shulman, 2011).

Neuroimaging studies in CRPS predominantly considered primary sensory and motor cortices as regions of interest (Di Pietro et al., 2013b, 2013a). However, one magnetoencephalography study showed weaker PPC activation in CRPS patients compared to healthy controls in response to tactile and nociceptive stimulation to the dorsum of the digits and hand, respectively. This activation difference could be a correlate of "neglect-like" symptoms, although these were not systematically assessed (Vartiainen et al., 2008). Functional magnetic resonance imaging studies of people with CRPS (as compared to healthy controls) demonstrated abnormal activation of PPC and supplementary motor cortices related to action observation (Hotta et al., 2017) and impaired reach to grasp movements (Maihofner et al., 2007). The findings are consistent with disrupted integration of visual and proprioceptive information, as found in neglect of body space (Committeri et al., 2007). Parietal dysfunction in CRPS has also been implied from behavioural research in which patients showed impairments on a test battery of cognitive functions known to be related to parietal lobe function (Joseph, 1990), such as spatial orientation, constructional abilities, object recognition, numerical and language processing, and imitating complex movements (Cohen et al., 2013; Maihofner & Peltz, 2011; Robinson et al., 2011).

Despite clinical and experimental evidence of changes in attention and visuospatial processing in CRPS, suggesting disruptions of parietal cortical networks, research looking into their neural correlates is scarce. The present study demonstrates behavioural evidence implying functional cortical changes in a case of CRPS without any known brain damage. The signs of patient's distorted body representation resembling misoplegia (shown by patients with right hemisphere damage; Bartolomeo et al., 2017; Critchley, 1974; Lewis et al., 2007), and a bias of exogenous attention in TOJs in body and near space are consistent with PPC dysfunction. Our observation of "reversal" of the direction of the attention bias suggests the role of plastic functional changes in parietal attentional networks that are not necessarily lateralised, in contrast to primarily structural deficits in post-stroke neglect.

4.4. Conclusions

Recognizing that the present findings may not apply to all individuals with CRPS, this longitudinal single case study demonstrates several ways in which neuropsychological changes can manifest in CRPS, and generates novel hypotheses that could be addressed in further research on larger patient samples. We conclude that cognitive spatial biases can be independent of response bias and low-level sensory deficits. Our patient showed significant spatial attention bias only in body and near space. However, it seems unlikely that this could be connected to body representation (as suggested by the "somatospatial inattention" hypothesis; Reid et al., 2016) or reduced movement of the affected limb (Punt et al., 2013) given that the direction of attention bias shifted between sessions whereas body representation and kinesiophobia remained similar. Further insights into the mechanisms of the distortions in spatial cognition in CRPS could be gained from investigating whether similar patterns of dissociations between body and near space versus far and imagined space replicate on a group level, or whether different patterns occur in other individuals with CRPS. The change from inattention to hyperattention to the affected side shown in this study suggests that attention bias in CRPS is not necessarily stable over time. This novel finding prompts further longitudinal research on cognitive changes in CRPS and how they might be relevant for treatments. Although there is substantial previous evidence of inattention to the CRPS-affected side (Bultitude et al., 2017; Filbrich et al., 2017; Moseley et al., 2009, 2012; Reid et al., 2016), our findings add to the existing literature that attention can be biased towards the affected side (Christophe, Delporte, et al., 2016; Jacquin-Courtois et al., 2017). This has implications for exploring individualized approaches to neurocognitive rehabilitation such as prism adaptation. Differential response to treatment dependant on the direction of attention bias could advance our understanding of the working mechanism of such interventions.

In line with previous CRPS research (Bultitude et al., 2017; Filbrich et al., 2017; Lewis & Schweinhardt, 2012; Moseley et al., 2009; Reid et al., 2016), we found distortions in body representation. Some changes in spatial attention and body representation also appear to be present in lateralised chronic pain syndromes other that CRPS (Förderreuther et al., 2004; Galer & Jensen, 1999; Kolb et al., 2012; Reinersmann et al., 2012), for example, phantom limb pain. Understanding the abnormalities in spatial attention and body representation in CRPS, and their neural correlates, could therefore facilitate our understanding of cognitive changes in other chronic pain conditions. Our patient showed deficits in processing incongruent information, which are similar to cognitive changes (impaired response inhibition) also found in other chronic pain conditions (Berryman et al., 2014). Thus, it appears that neuropsychological symptoms associated with pain are not necessarily unique to CRPS, yet they can be more pronounced in this population compared to other chronic pain conditions. It is yet unknown whether CRPS involves cortical aetiology that other pain conditions do not, or if this difference is related to general factors such as pain severity, number and dosage of medications, or sleep disruption specific to CRPS.

Although behavioural evidence for changes in attention and processing body-relevant information from the present and previous studies imply potentially abnormal parietal function in CRPS, research on the neural correlates of spatial attention bias in this population is lacking, in contrast to extensive investigations of sensory and motor cortex function (Di Pietro et al., 2013b, 2013a). Whether changes to spatial attention and body representation in CRPS are primary or secondary to its clinical signs calls for further examination of their mechanisms.

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Chapter 2 – Conclusions

This case study offers several noteworthy conclusions regarding how CRPS can affect cognition. The patient presented with non-spatially-lateralised difficulty with processing incongruent visual information. As discussed in Chapter 1, people with CRPS can show abnormal physiological responses when viewing ambiguous visual stimuli (Cohen et al., 2012; Hall et al., 2011) and report increased sensory disturbances when exposed to visuo-motor-proprioceptive incongruence (Brun et al., 2019). These findings could suggest that people with CRPS are particularly sensitive to sensory conflicts.

In Chapter 1, I discussed the limited sensitivity of traditional "pen-and-paper" tests of neglect for assessing spatial biases in CRPS. In line with this conclusion, the patient's performance on the Behavioural Inattention Test battery was normal, despite her apparent spatial biases on experimental test and upon confrontation testing. Although the sensitivity of confrontation testing could also be questioned, it shares certain features with the current experimental measure (temporal order judgements): the presentation of brief, lateralised, suprathreshold stimuli. Greater temporal demands and task difficulty can enhance a test's sensitivity to detect spatial attention deficits, for example, in chronic neglect patients (Bonato, 2012; Bonato & Deouell, 2013; Priftis et al., 2019). The following three chapters describe and implement such methods to study spatial cognition in CRPS and how it can be altered by prism adaptation.

Furthermore, this case study extends previous findings from the temporal order judgement tasks in CRPS by systematically controlling for response bias, visual impairment or any hemisensory deficits. Controlling for such potential confounds is considered best practice when studying spatial attention bias but has not commonly been implemented in previous studies of people with CRPS. In this case study, the demonstrated biases on the temporal order judgement task and confrontation testing cannot be attributed to these cognitive or lower-level sensory mechanisms, suggesting that they do reflect changes in lateralised spatial attention.

Although this study set out to test specific possible mechanisms of spatial biases, the results did not provide definitive insights into these. The patient presented with biases of covert spatial attention in bodily and near space, which are consistent with functional changes in posterior parietal cortex proposed in Chapter 1. The absence of any biases in far space or its mental representation agrees with the hypothesis that spatial deficits can arise due to limited movement in the affected side of near space. However, there was no evidence of any dissociations between the inferior and superior region of near space to further support this notion. In fact, in the third session, the patient showed increased attention to her affected side, which would counter the movement-related hypothesis. Although it is possible that the attentional shift was driven by adaptive re-engagement with the affected limb achieved through CRPS management programmes. Furthermore, there were no dissociations between biases in bodily space and near

space, and the shift from reduced to increased attention to the affected side occurred regardless of unchanged self-reported pain and distorted representation of the CRPS-affected limb. Thus, it is unlikely that CRPS pain or body representation distortion drive spatial attention biases. The magnitude and direction of spatial biases in temporal order judgements were consistent within each research session and across visual and tactile modalities in the third session, however, their direction was reversed between the second and third session. One possible explanation of this change is that additional injury of the ipsilateral lower limb between these two time points could increase attention to the affected side in this patient.

Individual variability in spatial attention bias can have implications for CRPS treatment, particularly the use of prism adaptation. The results of this case study indicate that attention bias might be independent of pain severity, nonetheless, prism adaptation appears to reduce pain in CRPS (Bultitude & Rafal, 2010; Christophe, Chabanat, et al., 2016; Sumitani, Rossetti, et al., 2007). This suggests that prism adaptation, if it is truly effective, might work through a mechanism other than normalising spatial attention, for instance, through correcting sensory-motor incongruence (see general introduction, and Chapters 3 and 5. Two of the following chapters aim to address this problem by proposing a protocol for (Chapter 3) and reporting results of (Chapter 5) a randomised controlled trial to test the effects of prism adaptation compared to sham treatment on pain and other CRPS symptoms, and to explore the hypothesised mechanisms of this intervention.

Chapter 3: Pain Reduction by Inducing Sensory-Motor Adaptation in Complex Regional Pain Syndrome (CRPS PRISMA): Protocol for a Double-blind Randomized Controlled Trial

Chapter 3 – Introduction

Over a century of research (von Helmholtz, 1909) on patients with hemispatial neglect and neurologically healthy volunteers demonstrates that the effects of prism adaptation are not limited to low-level sensory-motor function, but can extend to higher cognitive functions (Michel, 2016; Redding & Wallace, 1993). This highlights the promise of treatment not only for people with brain injuries, but also those with other pathological conditions, such as chronic pain. Despite encouraging preliminary evidence illustrated in the Introduction, so far there are no solid empirical grounds to support incorporating prism adaptation treatment into CRPS management programmes. Furthermore, as I summarised in Chapter 1, there is an increasing number of studies reporting null results regarding spatial biases in people with CRPS. In Chapter 2, I also showed that biases in spatial cognition can change independent of pain severity. These two points indicate that in addition to the need to robustly test prism adaptation treatment, there is also a need to further investigate the relationships between neuropsychological changes and clinical signs of CRPS. This understanding would be crucial for explaining the enigmatic working mechanisms of prism adaptation in CRPS, that is, how it can reduce pain. Addressing these issues could ultimately aid in developing new neurocognitive treatments, and improving or individually tailoring the existing interventions, to maximise their therapeutic effects. Having that in mind, in this chapter I present a protocol for a double-blind randomised controlled trial. The primary aim is to provide a robust test of the effects of prism adaptation treatment for CRPS, and the secondary aim is to assess and describe the patterns of neuropsychological abnormalities in people with CRPS compared to healthy individuals, and explore their clinical relevance.

To achieve these goals, the outcome measures proposed in the trial protocol comprise a battery of recommended patient-reported outcomes; clinical assessments of sensory, motor, and autonomic functions; and experimental computer-based and psychophysical measures of neuropsychological functions. Studies using some of these sensitive tests of spatial cognition (temporal order judgment, greyscales, and mental number line bisection tasks) and body representation (hand laterality recognition task) have previously provided evidence of reduced attention to the affected relative to unaffected side of space and distorted representation of the affected limb, as discussed in Chapter 1. The abovementioned tests of spatial cognition were also used in Chapter 2, with mixed results, demonstrating that people with CRPS might present with prominent spatial biases on one measure, but not others. Thus, several tests of different domains

of spatial cognition might be necessary to fully capture the hypothesised neuropsychological deficits in people with CRPS and how these might be affected by prism adaptation. Thus far, the temporal order judgement task appears to provide the most consistent evidence of spatial attention biases in CRPS. For the purpose of this study, I also adapted a landmark test of visual representation of space, similar to those previously used to study spatial cognition in patients with brain injury and amputees (Bisiach et al., 1998; Harvey et al., 1995; Makin et al., 2010). Relative to research on perceptual "neglect-like" symptoms in CRPS, experimental investigations into motor neglect are scarce and, thus far, directional motor deficits have not been tested. Therefore, to examine potential slowing of movements directed towards the affected relative to unaffected side of space, I adapted a spatially-defined motor function task, based on a method previously used in hemispatial neglect research (Sapir et al., 2007). The devised battery of neuropsychological tests allows me to assess any biases in visuospatial attention, mental representation of space, spatially defined motor function, and body representation.

Manifestation and treatment of CRPS should be considered within a biopsychosocial framework of chronic pain (Turk & Okifuji, 2002). While the clinical assessments, patient-reported psychological outcomes, and neuropsychological tests address the biological and psychological aspects of the condition, the social domain might seem overlooked. In chronic pain literature, several psychosocial and socioeconomic factors, including overprotective family members, lack of social support, low socioeconomic status, work conflicts, and compensation issues, among others, have been associated with poor pain and disability outcomes (Geertzen et al., 2006; Hoogendoorn et al., 2000). It has been suggested that socioeconomic factors associated with response to treatment or development of disability might be common across different chronic pain conditions (Turk & Okifuji, 2002). Yet their contribution to CRPS outcomes has been rarely considered or controlled for in the investigations of other prognostic factors (e.g. Bean et al., 2016; de Mos et al., 2009). Previous systematic reviews found no evidence of relationships between socioeconomic factors and CRPS (Marinus & Hilten, 2006; Wertli et al., 2013), and clinicians considered psychosocial factors much less relevant for poor CRPS prognosis than clinical factors (Brunner et al., 2011). However, there is some evidence of higher rates of CRPS among more affluent patients (Clement et al., 2017; Elsharydah et al., 2017), in contrast to poor outcomes predicted by lower socioeconomic status in other chronic pain conditions. Considering insufficient evidence of the relevance of socioeconomic factors for CRPS, substantial number of variables of interest included in the current trial protocol, and the scope of this study, socioeconomic measures are not included.

Statement of authorship

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Candidate's contribution to the paper (provide details, and also indicate as a percentage)	Monika Halicka considerably contributed to this manuscript (70%), being involved in formulation of ideas (55%), design of methodology (70%), and presentation of material in journal format (95%).		
Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.		
Signed	Monika Halicka	**Date**	10.05.2020

Pain Reduction by Inducing Sensory-Motor Adaptation in Complex Regional Pain Syndrome (CRPS PRISMA): Protocol for a Double-blind Randomized Controlled Trial

Monika Halicka[1,2], Axel D Vittersø[1,2,3], Michael J Proulx[2,4], and Janet H Bultitude[1,2]

[1]Centre for Pain Research, University of Bath, Claverton Down Road, Bath BA2 7AY, UK
[2]Department of Psychology, University of Bath, Claverton Down Road, Bath BA2 7AY, UK
[3]Department of Sport & Health Sciences, University of Exeter, Prince of Wales Road, Exeter, EX4 4SB, UK
[4]Centre for Real and Virtual Environments Augmentation Labs, Department of Computer Science, University of Bath, Claverton Down Road, Bath, BA2 7AY, UK

Corresponding author:

Monika Halicka
Email: m.halicka@bath.ac.uk
Phone: 01225 386226
Address: Department of Psychology, University of Bath, Claverton Down Road, Bath BA2 7AY, UK

Abstract

Background: Complex Regional Pain Syndrome (CRPS) presents as chronic, continuous pain and sensory, autonomic, and motor abnormalities affecting one or more extremities. People with CRPS can also show changes in their perception of and attention to the affected body part and sensory information in the affected side of space. Prism Adaptation (PA) is a behavioural intervention targeted at reducing attention deficits in post-stroke hemispatial neglect. PA also appears to reduce pain and other CRPS symptoms; however, these therapeutic effects have been demonstrated only in small unblinded studies. This paper describes the protocol for an ongoing double-blind, randomized, sham-controlled clinical trial that will evaluate the efficacy of PA treatment for CRPS. The secondary aims of the study are to examine the relationships between neuropsychological changes (such as spatial attention, space and body representation, and motor spatial performance) and clinical manifestations of CRPS, as well as symptom improvement.

Methods: Forty-two participants with upper-limb CRPS type I will undergo two weeks of twice-daily PA treatment or sham treatment. The primary outcome measures are current pain intensity and CRPS severity score, measured immediately before and after the treatment period. Secondary outcome measures include the results of self-report questionnaires about pain, movement, symptoms interference, and body representation; clinical assessments of sensory, motor, and autonomic functions; and computer-based psychophysical tests of neuropsychological functions. Data are collected in four research visits: four weeks and one day before treatment, and one day and four weeks after the end of treatment. Additional follow-up through postal questionnaires is conducted three and six months post-treatment.

Discussion: It is hypothesised that participants undergoing PA treatment, compared to those receiving sham treatment, will show greater reduction in pain and CRPS severity score, and improvements on other clinical and neuropsychological measures. Also, more pronounced neuropsychological symptoms are predicted to correlate with more severe clinical CRPS symptoms. This study will provide the first randomized double-blind evaluation of the therapeutic effects of PA that could be implemented as a rehabilitation method for CRPS, and will contribute to the understanding of how neuropsychological changes in body representation and attention pertain to the manifestation and treatment of CRPS.

Trial registration (27/03/2017): ISRCTN46828292 [1].

Keywords: Randomized Controlled Trial, Complex Regional Pain Syndrome (CRPS), Prism Adaptation, Pain, CRPS Symptom Severity, Attention, Body representation, Neuropsychology, Neglect, Protocol

1. Background

People with Complex Regional Pain Syndrome (CRPS) experience continuous pain and a range of sensory, autonomic, and motor signs and symptoms. The condition primarily affects one or more extremities, which can become swollen and present with asymmetric changes in hair, nail and skin growth, sweating, limb temperature, and skin colour. Further clinical features of CRPS include allodynia (non-nociceptive stimulation perceived as painful) and hyperalgesia (mildly noxious stimulation experienced as extremely painful), as well as motor disturbance in the affected limb (e.g., decreased range of movement, weakness, tremor, and muscle contractions [2, 3]). Although CRPS usually develops after an injury to the limb (e.g., a fracture [4]), it can also develop spontaneously [5], and the symptoms are disproportionate to any inciting trauma [3]. There is no known cause of CRPS, however, several pathophysiological mechanisms are suggested to play a role in the development and maintenance of this syndrome, including neuroinflammation, nociceptive sensitization, vasomotor dysfunction, and maladaptive neuroplasticity [2].

CRPS patients have shown reduced attention to tactile [6–8] and visual stimulation on the affected limb and in external space near it [9, 10]. These biases appear to be associated with the side of space in which the limb usually resides [7, 9] rather than a tendency to pay less attention to the affected body parts per se. These space-based attention changes resemble those found in post-stroke hemispatial neglect patients [11].

One emerging treatment for CRPS is Prism Adaptation (PA). PA is a form of a sensory-motor training used to reduce lateralised attention deficits in post-stroke hemispatial neglect. The treatment involves performing a pointing task while wearing goggles fitted with prismatic lenses that induce a lateral deviation of the visual image. Due to this visual shift, patients' pointing initially errs in the direction of prismatic displacement. With repeated movements, pointing becomes more accurate through an adjustment of pointing movements in the opposite direction to the optical shift, indicating a realignment of the sensory-motor reference frames [12, 13]. Once the goggles are removed, a negative after-effect is observed whereby pointing movements err in the opposite direction to the earlier optical shift. Using PA to induce pointing after-effects towards the neglected side reduces post-stroke hemispatial neglect [14–22].

The apparent attention bias in CRPS patients led to investigations of whether PA could also have therapeutic effects on chronic pain, as it does in post-stroke hemispatial neglect. Results of three studies have shown that PA performed with the affected hand to produce pointing after-effects towards the CRPS-affected side reduced pain and other CRPS symptoms [23–25]. One proposed mechanism of these apparent therapeutic effects is that PA reduces pain through correcting the lateralised spatial attention bias in people with CRPS. The magnitude of spatial biases has been previously linked to the severity of pain and other clinical signs of CRPS [7, 8, 26–30]. Moreover,

PA leading to the after-effects away from the affected limb appears to increase pain in CRPS [25], further supporting the role of lateralised attention effects. Another potential mechanism is that PA restores normal sensory-motor integration. Although empirical evidence to support this mechanism is limited, it has been proposed that discrepancies between motor commands and sensory feedback can contribute to pathological pain, including CRPS [25, 31–33].

However, the studies demonstrating therapeutic effects of PA in CRPS [23–25] included only small numbers of patients (13 in total across all three studies), no sham treatment conditions, and were not blinded. Thus, to date there are no sufficient grounds for implementing PA as a standard rehabilitation method for CRPS [12]. The aim of this study is to provide a robust evaluation of the effects of PA on CRPS through a double-blind, randomized-controlled trial.

1.1. Research questions and hypotheses

1.1.1. Primary research question (RQ) and hypothesis

RQ 1. Is two weeks of twice-daily PA treatment more effective in reducing pain and CRPS symptom severity than an identical regime using sham prism adaptation ("sham treatment")?

Sham prism adaptation has an identical procedure to PA treatment, except that pointing movements are performed without any optical deviation and therefore no adaptation takes place. This will allow us to dissociate the effects of the additional movement of the affected limb imposed by the treatment, to isolate the true effects of PA.

> Hypothesis: There will be greater reductions in pain and CRPS symptom severity in the participants who receive PA treatment compared to the participants who receive sham treatment.

1.1.2. Secondary research questions and hypotheses

RQ 2. Are there any improvements in other clinical signs of CRPS, psychological functioning, and neuropsychological symptoms following PA treatment?

In addition to the primary outcome measures of pain and CRPS symptom severity, we aim to evaluate the effects of PA treatment on secondary outcomes (listed below) that are relevant to participants' daily physical and psychological functioning, and for understanding the mechanisms of the therapeutic effects of PA (e.g., through establishing which neuropsychological symptoms might be affected by treatment).

> Hypothesis: Compared to the sham treatment group, participants in the PA group will have a reduction in spatial attention bias (consistent with its primary applications), as well as bias in cognitive representation of space and spatially-modulated motor function; body representation distortion (see [23]); emotional disturbance; fear of movement; average

pain, movement restriction, and symptoms interference; and sensory, motor, and autonomic signs of CRPS following treatment.

RQ 3. How long are any benefits sustained for after the cessation of PA treatment?

We will determine this through assessment of all primary and secondary outcomes immediately and four weeks after the completion of treatment, and through additional assessment of a subset of self-reported secondary outcomes at three and six months post-treatment. The time course of any improvements will be also analysed at more granular level through participants' daily subjective ratings of pain, range of movement, and the extent to which their symptoms interfere with daily life over a period of 10 weeks.

RQ 4. Are there factors that can predict the CRPS progression over time and / or the response to PA treatment?

Finally, the current study aims to explore potential predictors of the course of the disease and therapeutic response by tracking the symptoms of the same individuals over the course of 7.5 months. We plan to identify possible markers that would account for the individual differences in the progression of CRPS over time and / or in response to PA treatment. Due to insufficient evidence to support any specific predictions and limited sample size, we will perform exploratory analyses to address this research question. Factors such as demographic characteristics, pain intensity, CRPS symptom severity, sensory, motor and autonomic functions, and the extent of neuropsychological changes will be taken into consideration.

RQ 5. Are the neuropsychological changes in CRPS related to clinical signs and symptoms of CRPS?

A secondary aim of this study is to investigate the relationships between the severity of clinical symptoms of CRPS and the extent of neuropsychological changes in spatial attention, space and body representations, and motor functions.

Hypothesis: Baseline abnormalities in perception of and attention to the affected limb and its surrounding space in participants with CRPS (compared to the perception and attention of healthy control participants) will correlate with the severity of pre-treatment clinical symptoms.

2. Methods

2.1. Design

This study has a double-blind, randomized, sham-controlled design. The schedule of enrolment, interventions, and assessments is presented in Table 1 and consists of four in-person Research Sessions (RS), two weeks of twice-daily home-based treatment, and two sets of long-term postal follow-up questionnaires. After provisional eligibility assessment through a structured phone

interview, 42 participants with CRPS will undergo two baseline research sessions. Two baseline assessments (RS1 and RS2) are conducted to give an indication of normal fluctuations in CRPS symptoms (or lack thereof) prior to the treatment period. This will allow us to assess whether any change over the treatment period is meaningful, that is, greater than baseline fluctuations[1]. Research Session 1 (RS1) commences the timeline of the study at week 1 and includes in-person assessment of the eligibility criteria, informed consent, and collection of the outcome measures that are described in the "Measurements" section. Treatment allocation takes place 1-5 days before Research Session 2 (RS2), where the participants with CRPS are randomly allocated to one of the two groups of equal size: the PA treatment group or the sham treatment group. RS2 at the end of week 4 involves revisiting eligibility criteria and collecting outcome measurements. Immediately after completing RS2, the participants are instructed in how to carry out the treatment by a researcher who is not involved in any part of data collection. They then perform their first treatment under the guidance of that researcher. All other elements of the study (telephone screening, symptom assessment, experiment administration, and input of questionnaire data) are performed by researchers who are blind to the conditions that the participants have been allocated to. The treatment period spans weeks 5 and 6 of the study, where the participants perform twice-daily treatment in a self-guided manner. Outcome measurements are collected in two post-treatment assessments (RS3 and RS4) to evaluate differences in PA versus sham treatment effects, and whether any benefits of treatment are maintained at 4 weeks after treatment. The first post-treatment Research Session (RS3) takes place at the beginning of week 7 (i.e., the day immediately following the final treatment session). Research Session 4 (RS4) takes place in the beginning of week 11. Each research session is expected to last between 2 and 4 hours, including breaks between the assessments. During the first 10 weeks of the study, the participants also record their self-reported daily ratings of pain intensity, range of movement, and the extent to which their symptoms interfere with daily life in a provided logbook, which will allow us to track the time course of any changes between research sessions. Long Term Follow-Up 1 at 3 months (LTFU1; week 19) and Long Term Follow-Up 2 at 6 months (LTFU2; week 31) post-treatment are conducted through questionnaires sent and returned by post. RS3 marks the primary endpoint and LTFU2 marks the secondary and final endpoint of the study.

Deviations from the schedule of consecutive Research Sessions and Follow-Ups will be accepted within the following time windows: up to 2-weeks deferral of RS2 and RS4, up to 1-week deferral of RS3, up to 3-weeks deferral of LTFU1 and LTFU2. If the times that the participant can attend RS2 and RS3 are planned to be longer than 14 days apart, the participant would commence the

[1] Note that we will not exclude any participants based on having large fluctuations in symptoms between two baseline assessments (RS1 ad RS2), if they meet the CRPS diagnostic research criteria (see "Eligibility criteria" section).

treatment 2 weeks before RS3. If the participant already started the treatment and has to postpone RS3, they would continue the treatment until RS3.

Twenty-one healthy control participants are being recruited for a single research session to obtain normative data. They undergo testing only once and do not receive any treatment.

Table 1 *Schedule of enrolment, interventions, and assessments for the participants with CRPS*

	STUDY PERIOD								
	Enrolment	Baseline research sessions		PA treatment or sham treatment (14 days)		Post-treatment research sessions		Follow-up	
TIME POINT	Prior to Week 1 (phone)	Week 1 RS1	Week 4 RS2	Week 5	Week 6	Week 7* RS3	Week 11 RS4	Week 19 LTFU1	Week 31** LTFU2
ENROLMENT:									
Eligibility assessment	X	X	X						
Informed consent		X							
Allocation			X						
INTERVENTIONS (one of two, twice-daily):									
PA treatment OR				◆	◆				
Sham treatment				◆	◆				
ASSESSMENTS:									
Self-report questionnaires		X	X			X	X	X	X
Clinical assessments		X	X			X	X		
Computer-based tests		X	X			X	X		
Daily logbook***		◆	———	———	———	———	◆		

RS: Research Session; LTFU: Long Term Follow-Up (postal questionnaires only); PA: Prism Adaptation;
* Primary endpoint of the study.
** Secondary endpoint of the study.
*** Self-reported average levels of pain, range of movement and symptoms interference with daily life in the last 24 hours, rated daily on 0-10 Numeric Rating Scales

2.1.1. Setting of the study

All research centres and recruitment sites are located in the United Kingdom. The University of Bath is the main research centre and one of the research sites, and research sessions can also take place at the Universities of Oxford, Exeter, or Liverpool; or in participants' homes.

2.2. Participants

2.2.1. Eligibility criteria

2.2.1.1. Participants with CRPS

This study enrols both male and female individuals, who:

1) are willing and able to give informed consent to take part in the trial,
2) are aged 18-80,

3) have a diagnosis of CRPS type I based on the Budapest diagnostic research criteria [3] as assessed at RS1 and revisited at RS2,
4) have CRPS type I primarily affecting one upper limb,
5) have had CRPS for a minimum of 3 months at the time of RS1,
6) and report current pain intensity ≥2 on a 0-10 Numeric Rating Scale at RS1 and RS2.

Participants are excluded from the CRPS group if they:

1) lack sufficient English language ability to provide informed consent,
2) are classified as legally blind,
3) have a history of neurological disorder (e.g. stroke, neurodegenerative disease, or traumatic brain injury),
4) have CRPS meeting the Budapest diagnostic clinical or research criteria affecting both sides of the body[2],
5) report that they have confirmed presence of nerve damage (CRPS type II) based on the results of nerve conduction test,
6) have dystonia or any other physical limitation severe enough to prevent satisfactory execution of PA / sham treatment,
7) or have a severe psychiatric comorbidity (such as schizophrenia) that in the researchers' opinions would compromise participation in the study.

2.2.1.2. Healthy control participants

The inclusion criteria for healthy control participants of this trial are:

1) willingness and ability to give informed consent,
2) age 18-80,
3) and being neurologically healthy and without current or chronic pain.

Criteria that would exclude an individual from the study are:

1) insufficient English language ability to provide informed consent,
2) being classified as legally blind,
3) physical disability or injury limiting normal mobility,
4) or a history of a neurological or severe psychiatric illness.

[2] We will not exclude participants who have CRPS in ipsilateral lower limb if the upper limb is the primarily affected site and pain and other symptoms are not less severe than in the lower limb. Those participants, as well as participants with diagnoses of other chronic pain conditions (as long as these are less severe than CRPS), will complete the relevant self-reported outcome measures (i.e. questionnaires about pain) separately for the primary CRPS-affected upper limb, and separately for other chronic pain. We will measure the primary outcome of CRPS symptom severity only for the upper limb. Anecdotally, CRPS participants previously studied by our research group can easily differentiate CRPS pain and other symptoms in one extremity from another, and from other chronic pain conditions. Our primary analyses will only concern the pain and CRPS severity data regarding the CRPS-affected upper limb, however, data related to other pain might be used in exploratory analyses.

Each healthy control participant is matched to one participant with CRPS by sex, self-reported handedness prior to the onset of CRPS, and age (± 5 years).

2.2.2. Recruitment and participant retention strategies

The recruitment commenced on 31 March 2017 and is ongoing at the time of submission. People with CRPS are recruited through the National CRPS-UK Registry, Oxford University Hospitals NHS Foundation Trust, the Walton Centre NHS Foundation Trust, and other hospitals in the UK by post and clinicians' referrals. Information about the trial is also disseminated through word of mouth, print and online advertisements and articles, and social media. Trial webpages have been set up on the funder's and research centre's websites. All the above information channels provide potential participants with contact details of the authors, should they be interested in more information and / or taking part in the study.

To promote retention, participants are sent reminders before each RS and LTFU. Since recruitment takes place over a broad geographic area, their travel costs are reimbursed, or the research sessions are conducted in their own home. In recognition of the inconvenience of participation, which is heightened due to the burden of CRPS, participants receive a financial compensation of £250 for their time and contribution to the study once they complete RS4, and further financial compensation once they return the completed LTFU2 questionnaires by post (£50). Healthy control participants are reimbursed for their time and contribution at a rate of £10 per hour of their involvement.

Since the assessments and treatment are non-invasive and do not interfere with the participants' ongoing standard treatment, and there are potential benefits from taking part, we expect good participant retention. Some participants may directly benefit from reduction in pain and CRPS symptom severity due to treatment. All participants will have an opportunity to undergo the PA treatment after the trial is completed, should the trial support the effectiveness of the treatment.

In the event of the participant's withdrawal from the study, their data from any completed research sessions will be included in the analysis as far as possible. Participants who withdraw after RS2 will be considered lost to follow-up. For any participant who withdraws before RS4, an additional participant will be recruited to the trial such that there will be 42 full datasets for RS1-RS4. Recruitment will be terminated only once we reach sufficient number of participants in each treatment arm, or if we are not able to collect 42 full datasets for RS1-RS4 by 1 March 2019. To address any potential selection bias, we will use intention to treat as our primary analysis, and per-protocol as supportive analysis (see "Treatment outcome analyses" section). Should participants deviate from the intervention protocol (e.g., missed treatment sessions), the number of logged treatment sessions can be used as a possible covariate in the final analyses.

2.3. Randomisation

Treatment allocation is conducted by method of randomisation with minimisation of baseline (RS1) group differences. Eligible participants with CRPS are allocated in equal numbers to one of the two treatment groups: PA treatment group or sham treatment group. Group allocation is performed using MINIM computer program [34] by a researcher who is not involved in data collection (JHB). Following allocation of the first participant using simple randomisation, allocation of each next participant considers the characteristics of those participants who are already allocated. Specifically, the minimisation procedure controls for the baseline (RS1) participant characteristics that are listed in Table 2. In the event of participant's withdrawal after treatment allocation, but before RS3, their data shall be removed from the minimisation procedure and any subsequent participants recruited for the trial shall be allocated based on the current number and pool of participants in each treatment arm. This strategy is implemented to assure equal numbers of full datasets with any post-intervention data in the two groups and minimisation of baseline between-group differences.

Table 2 *Criteria for minimisation as recorded in RS1*

Factor	**Weight**	**Categories**
Current pain intensity (0 – 10 Numerical Rating Scale)	2	≤ 6 > 6
CRPS severity score (1 - 16) [35]	2	≤ 12 > 12
Primarily affected arm	1	Left Right
Pre-CRPS dominant hand (writing)	1	Left Right
Sex	1	Male Female
Age	1	18 - < 40 40 - < 61 61 - 80
Presence of CRPS in body parts other than the primary affected arm	1	Yes No
Presence of other non-CRPS pain	1	Yes No
CRPS duration	1	< 1 year 1 - < 5 years 5 - < 10 years ≥ 10 years

2.4. Treatment

Participants in the PA treatment group are provided with welding goggles fitted with 35-diopter (Δ) Fresnel lenses that induce a visual shift of approximately 19° away from the CRPS-affected

side. The optical displacement is of a similar magnitude as in previous CRPS studies that reported significant reductions in pain [23–25]. In contrast, no pain reduction was observed when a CRPS patient underwent two weeks of PA using lenses that shifted the visual image only by 5° [25]. Furthermore, prisms strength of 10°-15° was found to be sufficient to induce lasting amelioration of hemispatial neglect after brain injury [15, 18, 19, 36, 37], whereas weaker prisms did not improve neglect [38]. During each treatment session, the participant is seated in front of a vertical surface, such as a wall, upon which an A4 laminated page in landscape orientation is positioned. The page displays two visual targets (red circles 2cm in diameter), in each top corner. The page is mounted approximately at eye-level, hence targets are located 12.5cm (approximately 10°) to the left and to the right of the participant's body midline. The distance between their torso and the wall is established individually, such that the participant can touch the targets with an almost fully extended arm (approximately 60cm). Participants put on the goggles and use their CRPS-affected arm to perform a total of 50 pointing movements (a number sufficient to induce sensory-motor adaptation [16]), alternating between the two targets (25 per side) and returning the pointing hand to their chest between each movement. The participants are instructed and trained to move as quickly as possible, and the goggles occlude the vision of the participant's arm for approximately the first half of the movement. Both these steps limit on-line correction of movement trajectory (strategic component of PA) and reinforce adaptive realignment, which is thought to maximise the effects of PA [13, 39, 40]. One treatment session takes approximately 5 minutes. The participant performs the treatment once under the guidance of an experimenter, and then twice daily for two weeks in a self-guided manner in their own home (giving a total of 29 treatment sessions). The intensity and duration of the treatment regime have been established based on previous studies evaluating the effects of PA on attention in hemispatial neglect following stroke, and on pain in CRPS. In particular, previous studies suggest that repeated sessions of PA are required to obtain a significant reduction in CRPS symptoms [23, 25] and that intense treatment (2 sessions a day for 4 days or more) produces symptom reduction that is sustained for at least two weeks post-treatment [23, 24].

Participants in the sham treatment group carry out the same procedure as the PA treatment group, except they are provided with goggles fitted with neutral lenses that do not induce optical deviation of the visual field. This is a standard control treatment for PA [18, 41]. Both prismatic and neutral lenses distort the acuity and clarity of vision, and both sets of goggles occlude the first part of the reaching movement. This factor ensures similarity of the two treatment arms in all aspects of the treatment aside from the sensory-motor adaptation.

To improve their adherence to the treatment protocol the participants receive in-person training, in which they complete the first treatment session guided by JHB or ADV, who ensure participants' competence in performing the exercise according to the protocol. Furthermore, participants are provided with written instructions and a video tutorial. The researcher who trained

them in the treatment is also available to address any questions or concerns about the procedure by phone or email. In order to monitor participants' compliance and adherence, they keep a daily logbook throughout the treatment period, in which they record the time and duration of each treatment session. We will report the adherence to treatment as a percentage of participants in each treatment group who did not miss more than 6 treatment sessions. The extent of exposure in each group will be reported as average number of logged treatment sessions. Protocol deviations are defined as missed or additional treatment sessions, and sessions for which logbook entries suggest that anything other than the trained procedure has been used. We will report the total number of treatment sessions per group in which deviations other than missed or extra sessions are suspected. We will also compare the average number of logged treatment sessions between the two groups, and if significantly different, the number of logged treatment sessions will be used as a covariate in the analyses of the primary outcomes.

The participants are instructed to continue their standard pharmaceutical, physical, and / or other treatments during the trial, and are encouraged not to make any significant alterations to these treatments (e.g., major changes in medication, commencing new physiotherapy programmes). Medications and other treatments are noted during every research session to monitor any changes.

Criteria for discontinuing the allocated treatment before the 2 weeks have elapsed are a participant's withdrawal from the study or reports of experiencing an increase in CRPS symptoms that significantly heightens their discomfort or distress. As the treatment procedures require repeated movements of the CRPS-affected arm, participants may experience pain related to movement. However, this is expected to be temporary and no greater than the pain that could accompany standard physiotherapy or daily activities. To date, there have been no publications reporting serious adverse events related to PA in healthy controls or clinical populations (patients with stroke, Parkinson's disease [41], or CRPS). In one case study exploring the effects of different PA directions and strengths, one CRPS patient experienced a small, temporary increase in pain when they performed PA using optical deviation towards the affected side [25]. Similar events in the current study are highly unlikely, as all PA is conducted with optical deviation away from the CRPS-affected side, i.e., in the direction thought to achieve therapeutic effects. Each participant is assigned their own dedicated set of prism goggles in a bag labelled with their participant code. The direction of optical deviation is independently checked by two people before the goggles are placed in a labelled bag. Any unexpected serious adverse events related to the administration of any study procedures will be reported to the researcher responsible for blinding (JHB) who will then make any decisions about discontinuing an individual's participation and / or the trial, in consultation with the protocols for dealing with adverse events as outlined by the Research Ethics Committees.

Table 3 *Measures*

Measurement domain	Measurement tool	Time points	Research question* / justification for use
Self-report measures			
Pain and symptom interference	Current pain intensity (Item 6 of the Brief Pain Inventory)	Weeks 1, 4, 7, 11, 19 & 31	RQ1, RQ3, RQ4, RQ5; group matching on baseline pain
	Brief Pain Inventory† (BPI; short form; pain intensity and interference) [42]		RQ2, RQ3, RQ4, RQ5
	Pain Detect Questionnaire [43]		RQ2, RQ3, RQ4, RQ5
	Average pain intensity (Logbook)	Weeks 1 to 11 (daily)	RQ2, RQ3
	Average symptom interference (Logbook)		RQ2, RQ3
Physical functioning	Average range of movement (Logbook)	Weeks 1 to 11 (daily)	RQ2, RQ3
	Edinburgh Handedness Inventory (current and change) [44]	Week 1	RQ4, RQ5; participant characteristics
Body representation	Bath CRPS Body Perception Disturbance Scale (BPDS) [45]	Weeks 1, 4, 7, 11, 19 & 31	RQ2, RQ3, RQ4, RQ5
Emotional functioning	Tampa Scale for Kinesiophobia† [46]	Weeks 1, 4, 7, 11, 19 & 31	RQ2, RQ3, RQ4, RQ5; group matching on baseline fear of movement
	Profile of Mood States [47]		RQ2, RQ3, RQ4, RQ5; group matching on baseline mood disturbance
	Revised Life Orientation Test [48]	Week 1	RQ4; group matching on baseline levels of optimism
Treatment expectations	Patient-Centred Outcomes Questionnaire [49]	Week 1	RQ4; group matching on expectations of treatment outcomes

Measurement domain	Measurement tool	Time points	Research question* / justification for use
Impression of treatment outcome	Patient's Global Impression of Change [50]	Weeks 7, 11, 19 & 31	RQ2, RQ3
Treatment adherence	Treatment sessions (Logbook)	Weeks 4 to 6 (twice-daily)	Monitoring treatment adherence
Clinical assessments			
CRPS diagnosis	Budapest diagnostic research criteria assessment [51]	Weeks 1, 4, 7 & 11	Verification of CRPS diagnosis and assessment of eligibility
Symptom severity	CRPS severity score [52]	Weeks 1, 4, 7 & 11	RQ1, RQ3, RQ4, RQ5; group matching on baseline symptom severity
Autonomic functions	Limb temperature asymmetry	Weeks 1, 4, 7 & 11	RQ2, RQ3, RQ4, RQ5
	Oedema		
Motor functions	Grip strength	Weeks 1, 4, 7 & 11	RQ2, RQ3, RQ4, RQ5
	Δ Finger-To-Palm distance (ΔFTP)		
Sensory functions	Mechanical Detection Threshold (MDT)	Weeks 1, 4, 7 & 11	RQ2, RQ3, RQ4, RQ5
	Mechanical Pain Threshold (MPT)		
	Mechanical Allodynia		
	Two-Point Discrimination [53]		
Computer-based tests of neuropsychological changes			
Visuospatial attention	Visual Temporal Order Judgement (TOJ) [9]	Weeks 1, 4, 7 & 11	RQ2, RQ3, RQ4, RQ5
	Landmark task [54]		
	Greyscales task [55]		

Measurement domain	Measurement tool	Time points	Research question* / justification for use
Mental representation of space	Mental Number Line Bisection task [56]	Weeks 1, 4, 7 & 11	RQ2, RQ3, RQ4, RQ5
Spatially-defined motor function	Directional Hypokinesia [57]	Weeks 1, 4, 7 & 11	RQ2, RQ3, RQ4, RQ5
Body representation	Hand Laterality Recognition task [58]	Weeks 1, 4, 7 & 11	RQ2, RQ3, RQ4, RQ5

* RQ1, effects of treatment on the primary outcome measures; RQ2, effects of treatment on the secondary outcome measures; RQ3, time course / duration of any changes; RQ4, predictors of CRPS progression over time and/or response to treatment; RQ5, baseline abnormalities in neuropsychological functions in participants with CRPS compared to pain-free controls, and their relationships with clinical signs of CRPS (only Week 1 data).

† Brief Pain Inventory interference subscale and Tampa Scale for Kinesiophobia are also considered proxy measures of physical functioning.

2.5. Measurements

Tests and measures used in the current study and time points at which they are administered are listed in Table 3. These are categorised as self-report questionnaires, clinical assessments, or computer-based tests.

2.5.1. Baseline descriptors

Age, sex, and handedness of all the participants are recorded as demographic characteristics. An interview regarding their medical history is conducted to collect information about the date and type of any inciting injury or insult, CRPS duration in months from diagnosis to RS1, the presence of CRPS in body parts other than the primarily affected upper limb, the presence of non-CRPS pain conditions and other co-morbidities, and current treatments.

A hand laterality index is calculated using the Edinburgh Handedness Inventory [44] in RS1. The scoring can range from -100 (extreme left-handedness) to 100 (extreme right-handedness). All participants respond regarding their current hand preference, and the participants with CRPS additionally complete another version of the Edinburgh Handedness Inventory based on their recalled hand preference prior to the onset of CRPS symptoms. A "change in handedness" score (Handedness after CRPS – Handedness before CRPS) is calculated to give an approximation of the functional impact of the CRPS.

2.5.2. Primary outcomes

A change between RS2 (immediately before the commencement of treatment) and RS3 (immediately after the end of the treatment period) in current self-reported pain intensity and CRPS severity score [35, 52] are the primary outcomes. People with CRPS consider pain relief to be the highest priority for recovery [59], and pain intensity is the most common primary outcome in chronic pain trials [60]. Current pain intensity is measured using item 6 of the Brief Pain Inventory (BPI; short form) [42], which is a Numerical Rating Scale (NRS) ranging from 0 – "no pain" to 10 – "pain as bad as you can imagine". The BPI has high reliability [42]. In addition to pain, CRPS involves a range of other debilitating symptoms, some of which were also affected by PA in previous studies [23, 25]. Therefore, we included a comprehensive measure of symptoms severity as the second primary outcome. The CRPS severity score assessment protocol follows the 16-points scoring system published by Harden and colleagues [35]. This continuous index of CRPS symptom severity has good discrimination abilities, concurrent validity and adequate sensitivity to change [35, 52], and has been recommended as one of the core outcome measures for CRPS clinical studies [61].

2.5.3. Secondary outcomes

2.5.3.1. Self-report questionnaires

There is a lack of validated outcome measures for CRPS (however, see recently published recommendations [62]). Therefore, the choice of the measures for the current trial was guided by general recommendations of core outcome measures for chronic pain clinical trials (IMMPACT; [60]) and the existing literature on CRPS implicating other relevant questionnaires.

There are 10 self-report questionnaire measures of pain, physical and emotional functioning, body representation, expectations about treatment, and impressions of treatment outcome. The BPI [42], Pain Detect Questionnaire [43], Bath CRPS Body Perception Disturbance Scale (BPDS; [45]), Tampa Scale for Kinesiophobia, and Profile of Mood States [47] are completed in every research session and long-term follow-up (RS1-RS4, LTFU1-LTFU2). A Revised Life Orientation Test [48] and a Patient-Centred Outcomes Questionnaire [49] are administered only in RS1. The Patient's Global Impression of Change questionnaire [50] is completed only at post-treatment research sessions and long-term follow-ups (RS3-RS4, LTFU1-LTFU2). Finally, a daily logbook of self-reported average pain, range of movement, and symptom interference is kept by the participants during the baseline, treatment, and post-treatment periods (i.e., every day for the 10 weeks that elapse between RS1 and RS4).

Participants use the short-form of the BPI [42] to rate their pain intensity (current, average, and worst and least pain over the last 24 hours) and the extent to which pain interferes with their physical, social and psychological functioning on 0-10 NRSs (0 – "no pain" or "does not interfere"; 10 – "pain as bad as you can imagine" or "completely interferes", respectively). The pain intensity component of BPI can result in an average score between 0 and 10; an average interference component score can also range from 0 to 10. The Pain Detect Questionnaire is a validated measure of the neuropathic features of experienced pain [43] scored from -1 to 38, with higher scores indicating a greater neuropathic component of pain.

The BPDS [45] includes seven self-reported items to assess subjective detachment, awareness, attention to, and feelings about the CRPS-affected limb; the perceived changes in size, temperature, pressure, and weight of the limb; and any desire to amputate the limb. The BPDS includes a mental imagery task in which the mental representation of both limbs (affected and unaffected) is sketched by a researcher based on the participants' description. Total score ranges from 0 (no disturbance) to 57 (most severe disturbance of body perception). Since BPDS is not a validated measure, normative data is also collected from healthy control participants who are responding to the self-report components regarding the limb that corresponds to the CRPS-affected limb of their matched participant with CRPS.

The Tampa Scale for Kinesiophobia [46] is administered to measure pain-related fear of movement and re-injury. The participants choose the extent to which they agree with each of 17

statements about fear of movement and physical activity that could (subjectively) cause pain and / or injury (1 – "strongly disagree", 4 – "strongly agree"). The final score varies from 17 to 68 points, with higher numbers indicating more severe kinesiophobia. The Tampa Scale for Kinesiophobia is included as a measure of the likely extent to which participants use their affected limb and their beliefs and emotions about those movements.

Considering that mood can exert effects on pain [63–65] and attention [66–68], the Profile of Mood States is administered in the current trial to verify that the two treatment groups are matched according to mood disturbance, and to enable evaluation of whether treatment results in any significant differences in mood improvements between the groups. The Profile of Mood States is a 64-item scale indicating the extent to which the respondent is experiencing various transient, distinct mood states (1 – "not at all", 5 – "extremely"). High reliability and validity of Profile of Mood States [47, 69] has been reported. This measure is also completed by healthy control participants at a single research session.

The Revised Life Orientation Test [48] assesses levels of optimism and pessimism. Participants rate to what extent they agree with 10 statements on a scale from 0 – "strongly disagree" to 4 – "strongly agree". The Patient Centred Outcomes Questionnaire [49] is also administered to measure patient-centred expectations and criteria for success in chronic pain treatment. Rating scales from 0 to 10 are used to indicate the usual, desired, expected and considered successful levels of pain, fatigue, emotional distress, and interference with daily activities (0 – "none", 10 – "worst imaginable"), and the importance of improvement in each of these areas (0 – "not at all important", 10 – "most important"). The decision to include the Revised Life Orientation Test and the Patient Centred Outcomes Questionnaire in the current trial was driven by the fact that optimism and expectations of outcome have been known to influence the success of novel treatments [70–72]. Thus, it is important to confirm that the two treatment groups are matched on these extraneous factors, or to include these variables as covariates in the analysis of outcome measures if they are not.

The participants keep daily logbooks for weeks 1-11 in which they use 0-10 NRSs to record their average level (over the preceding 24 hours) of pain (0 – "no pain at all", 10 – "pain as bad as it could be"), the range of movement in the affected arm (0 – "no movement at all", 10 – "normal movement"), and the degree to which their symptoms have interfered with their daily life (0 – "no interference at all", 10 – "complete interference"). These measures are designed to track the time-course of any change in pain, movement, and interference during the first 10 weeks of the study (i.e. four-week baseline period, two-week treatment period, and four-week immediate post-treatment period).

Finally, the Patient Global Impression of Change questionnaire [50] is administered to measure participants' impression of how much their symptoms have changed due to treatment. It produces a single rating on a scale from 1 – "no change" to 7 – "a great deal better". The Patient Global

Impression of Change is a widely recommended measure of perceived global improvement and satisfaction with treatment [60, 62].

2.5.3.2. Clinical assessments

The clinical measures include examination of CRPS signs and symptoms, sensory thresholds, autonomic changes, and motor functions. Participants with CRPS undergo all clinical assessments in RS1-RS4, whereas healthy control participants undergo the same clinical assessments during a single research session. Locations for sensory testing are the most painful site on the CRPS-affected limb and the corresponding site on the unaffected limb, always beginning with the unaffected limb so that participants can be familiarised with the test procedures and sensations before the tests are administered on their painful limb. For sensory testing in control participants, measures taken from the limb corresponding to the CRPS-affected limb of their matched participant with CRPS are compared to measures taken from the other limb.

CRPS diagnosis is confirmed in RS1 and RS2 during the baseline period, before commencement of the treatment, based on the Budapest research criteria [51]. These criteria are also assessed in the post-treatment period (RS3-RS4) to determine if the participants still meet the CRPS diagnosis.

The severity of symptoms is assessed and quantified as CRPS severity score in RS1-RS4, according to a recently validated protocol [35, 52]. Each of the 16 items is recorded as present ("1") or absent ("0") based on the self-reported symptoms and the signs confirmed at the time of examination through sensory testing, visual, and manual assessments. These include continuing, disproportionate pain; allodynia; hyperalgesia and / or hypoesthesia; temperature, colour, and sweating asymmetry; oedema; dystrophic changes; and motor abnormalities. Summed scores indicate the overall CRPS severity score. Where possible, criteria are evaluated based on a comparison between the affected and unaffected upper limb for a sign to be classified as present, including objective quantification of limb temperature asymmetry, oedema, muscle weakness, and active range of movement.

Photographs of the dorsal and palmar surface of both hands and forearms are taken so that the presence of skin colour and trophic changes can be double-scored by a researcher who is not involved in data collection and who is blind to the time point at which the photographs were taken, to which limb is affected by CRPS, and to which group the participant is allocated. Video recordings of both limbs performing the movements of fist closure and opening, wrist flexion and extension, and radial and ulnar wrist deviation are taken so that the motor abnormalities can be double-scored according to the same protocol. We will use Cohen's kappa statistic to report inter-rater agreement.

An infrared thermometer is used to measure temperature asymmetry. Temperature measurements are taken to the nearest 0.1°C from the dorsal and palmar surface of both hands (over the thenar

muscle) and the centre of the region of worst pain as indicated by the participant. An arithmetic mean of the 3 measurements on each limb is calculated. According to the Budapest diagnostic criteria [51], an absolute difference between the affected and unaffected side greater than 1°C is classed as a temperature asymmetry. When available, thermal images of both limbs are additionally taken (camera FLIR T620 that is sensitive to changes in temperature as small as 0.04°C).

Oedema is measured using the figure-of-eight procedure that uses a soft tape measure. The detailed protocol for hand and wrist size measurement is described elsewhere [73]. This measure has excellent intra- and interrater reliability and concurrent validity compared with water volumetry [74]. Hand size is calculated as an arithmetic mean of 3 measurements performed on each hand. Presence of asymmetric oedema is considered if the average measure taken from the CRPS-affected hand is at least 0.56cm larger compared to the unaffected hand, which was suggested to be a clinically relevant difference in a previous study [75].

Grip strength is measured as a marker of muscle weakness, using an electronic hand dynamometer (Constant, model 14192-709E). Participants are seated in a chair with their elbows flexed at 90°, forearms in neutral position, and wrists at between 0 and 30° extension. They are instructed to squeeze the dynamometer's handle as hard as they can and perform three such trials with each hand, alternating between the hands and allowing a pause of at least 15 seconds between each trial. An arithmetic mean of the 3 measurements (kg force) for each hand is calculated. Muscle weakness of the affected hand is indicated if the ratio of grip force in the affected to unaffected side is smaller than 0.95 for left-handed participants or smaller than 0.85 for right-handed participants. These criteria take into account the normal difference between dominant and non-dominant hands for left- and right-handed individuals [76, 77].

Active range of movement in the hands is assessed by measuring a change in Finger-To-Palm (ΔFTP) distance (cm). A detailed measurement protocol is described elsewhere [78]. ΔFTP is an index of the extent to which a person can fully flex their fingers (e.g., to make a fist) relative to the extent to which they can extend them (e.g., to make their hand flat). ΔFTP was selected as a measure of range of movement as it takes into account both these aspects of motor function, unlike classic FTP that only regards the maximum flexion. A significant decrease in the range of movement in the affected hand is defined as $\Delta FTP_{affected} / \Delta FTP_{unaffected} < 0.9$.

In addition to those limb differences that are assessed through clinical examination for the CRPS severity score, differences between the affected and unaffected limbs are also objectively quantified through elements of a standard Quantitative Sensory Testing (QST) procedure to assess hypoesthesia, pinprick hyperalgesia, and allodynia. Participants undergo the assessment of Mechanical Detection Threshold (MDT) that follows the standardized protocol [79] using von Frey filaments of 0.008g to 300g force (Bioseb, model Bio-VF-M). Then the ratio of thresholds for affected vs. unaffected side is derived $[(MDT_{affected}-MDT_{unaffected})/MDT_{affected}]$. A positive score

indicates hypoesthesia (increased tactile detection threshold) on the affected side. Based on relative QST reference data comparing both sides of the body, hypoesthesia is confirmed if the ratio is ≥ 0.38 [80]. We also assess Mechanical Pain Threshold (MPT) according to the standardized protocol [79] on both limbs, using pinprick stimulators of 8mN to 512mN intensities (MRC Systems PinPrick Stimulator Set). A positive thresholds ratio [($MPT_{unaffected}$-$MPT_{affected}$)/$MPT_{unaffected}$] indicates hyperalgesia (decreased pain threshold) on the affected side. Hyperalgesia is confirmed if the ratio is ≥ 0.4, based on relative QST reference data comparing both sides of the body [80]. Allodynia is examined using a procedure adapted from the dynamical mechanical allodynia test of the QST [79]: the cotton ball, Q-tip and brush (MRC Systems PinPrick Stimulator Set) are applied to the skin five times each, in a random order, with a single 1-2cm long sweeping motion lasting approximately 1 second. Participants rate each sensation on a scale from 0 – "no pain, no sharp, pricking, stinging, or burning sensation" to 100 – "most intense pain sensation imaginable". Any sharp, pricking, stinging, or burning sensation is defined as painful and given a rating above 0. Allodynia is quantified as an arithmetic mean of 15 ratings on each limb. Its presence is indicated by scores greater than zero.

A Two-Point Discriminator disk (Exacta, North Coast Medical) is used to record tactile discrimination thresholds [53]. The participant's index fingertip is touched either with one tip or two tips of the disk for 3 seconds per touch, with consistent pressure, and while the participant has their eyes closed. On each trial, participant reports whether they perceived touch on one point or two points of their finger. The procedure starts with two points separated by 7mm distance, and the distance between points is increased or decreased (down to a single tip) across trials according to the staircase procedure. For example, if the participant initially reports two touches, smaller distances are applied until the participant reports the sensation of only one point. The distance is then increased until a sensation on two points is reported again. The procedure continues until 5 subthreshold and 5 suprathreshold values are obtained. The tactile discrimination index is calculated as a geometric mean of these 10 turning points for each hand. To quantify the difference between the two sides of the body, we derive the tactile discrimination thresholds ratio [(affected-unaffected)/affected]. Positive score indicates less precise tactile discrimination ability on the affected limb.

2.5.3.3. Computer-based / psychophysical tests

Six computer-based measures are used in the present study to assess the following neuropsychological functions: visuospatial attention, cognitive representation of space, spatially-defined motor function, and body representation. To test for spatial attention bias in near space, we administer versions of three tasks that have been used to measure spatial attention in hemispatial neglect: a visual Temporal Order Judgement (TOJ) task [9], a Landmark task [54], and a Greyscales task [55]. The fourth task is a Mental Number Line Bisection task, which measures the mental representation of space [56, 81]. The fifth task is a Directional Hypokinesia

task, a measure of motor "neglect-like" impairment. The final computer-based task is a Hand Laterality Recognition task, which is thought to be indicative of body representation [58].

All measures presented in this section are collected in RS1-RS4 from the participants with CRPS and during a single research session from healthy control participants. Hand and side of space for all tasks are coded as affected or unaffected (for controls, the "affected" and "unaffected" hand / side is coded based on their matched participant with CRPS). Each task is preceded by a short practice session to familiarise the participant with the task. If they do not appear to follow the instructions during practice, these are explained again, and the practice is repeated.

2.5.3.3.1. Visuospatial attention

The following three computer-based tests are used to measure visuospatial attention: the visual TOJ task, the Landmark task, and the Greyscales task.

2.5.3.3.1.1. The visual TOJ task

TOJ tasks are sensitive measures of covert spatial attention, used both in clinical populations [82–88] and healthy people [89–93]. The usual procedure involves presenting pairs of identical stimuli, one on each side of space, with different onsets but the same duration. The participant's task is to report which of the two stimuli they perceived first. According to the prior entry hypothesis [94], stimuli that are subject to greater attention are perceived earlier relative to stimuli that are subject to lesser attention. The TOJ task takes advantage of this premise. The visual variant of the TOJ used in this study is similar to that described in a previous article [9]. The participants keep their hands uncrossed on their laps under the table, and have their head stabilised by a chinrest. They are instructed to maintain their gaze on a black fixation point (3mm in diameter), approximately 28cm from their torso, located in the centre of a 46.5 x 35.5cm white board laid on a table. Pairs of brief (10ms) red light stimuli (3mm in diameter) are presented using laser pointers controlled via an Arduino platform that is integrated with PsychoPy software [95]. The lights are presented 9cm (approximately 18°) to the left and 9cm to the right of the fixation point (one on each side), using a range of ten temporal offsets: ±10, ±30, ±60, ±120 and ±240ms (with negative numbers representing the trials in which the light on the affected side appeared first). Each temporal offset is presented 15 times in pseudorandom order, giving a total of 150 trials. To account for any response bias [96] the participants complete the TOJ task once while indicating which of the two lights appeared first, and a second time while indicating which light appeared second (order counterbalanced between participants). Participants' verbal responses ("Left" or "Right") are inputted via the computer keyboard by the researcher. The relative number of left-right responses to different offsets of the stimuli is re-expressed as the number of affected-unaffected responses. To derive the Point of Subjective Simultaneity (PSS) for each participant and each condition, these data are then fitted with a cumulative Gaussian using a criterion of maximum likelihood. The PSS expresses the amount of time (ms) by which the light that appears in the affected side of space should precede (negative PSS values) or follow (positive PSS values)

the light that appears in the unaffected side of space for the two stimuli to be perceived as simultaneous. For the analysis, PSSs from the two response blocks (which light appeared first or second) will be averaged to obtain a single index of attention bias. A negative PSS value indicates a bias of attention away from the affected side, whereas a PSS value of 0 indicates equal distribution of attention to both sides of space.

2.5.3.3.1.2. The Landmark task

In addition to the TOJ task, participants complete four tasks involving presentation of visual stimuli on a computer screen. For these, participants are seated with their head in a chinrest that is aligned with the centre of the screen. Stimuli are presented on a laptop touch screen (34.5cm x 19.4cm size, 1920 x 1080 pixels resolution) using PsychoPy software [95] on the Windows 10 operating system. The laptop screen is positioned at a viewing distance of 50cm. The responses are recorded using a custom-made button box positioned such that the buttons are aligned vertically.

We use a modified version of a Landmark task to measure bias in attention to or the representation of relative horizontal distance in near space. The task is adapted from a previous study [54] and involves simultaneous presentation of two stimuli ("landmarks"; white circles 1.1° in diameter) to the left and to the right of a central fixation cross. The total distance between the two landmarks is kept constant across trials (15°), however, their position relative to the fixation cross varies by 0.1° increments from ±8.1° to ±6.9° away from the fixation cross in the horizontal plane (Figure 1). Thus, there are 6 stimulus pairs in which the right landmark is closer to the fixation cross, 6 stimulus pairs in which the left landmark is closer, and 1 stimulus pair in which the distance of both landmarks from the fixation cross is equal. Each stimulus pair is presented 15 times during one block resulting in 195 trials per block, presented in pseudorandom order. The participant is instructed to maintain their gaze on a white, 1.4° high fixation cross presented in the centre of a grey screen. After 500ms, the fixation cross is joined by the two stimuli which are displayed for 300ms. Then a 200ms mask is presented, consisting of a white 1.6° high line extending horizontally across the entire screen, with a grey fixation cross in the same location as the previous white one (Figure 2).

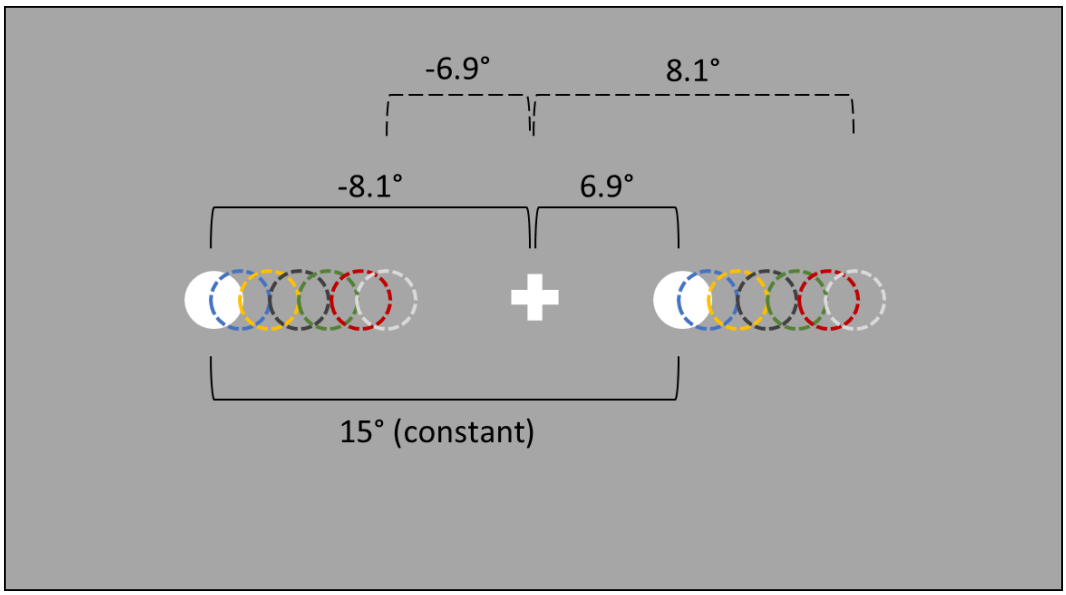

Figure 1. Representation of the stimuli in the Landmark task. White filled circles represent the stimulus pair in which the left landmark is farther from the fixation cross (-8.1° away) and the left landmark is closer (6.9° away). Circles with dashed lines in matched colours represent other possible stimulus pair locations.

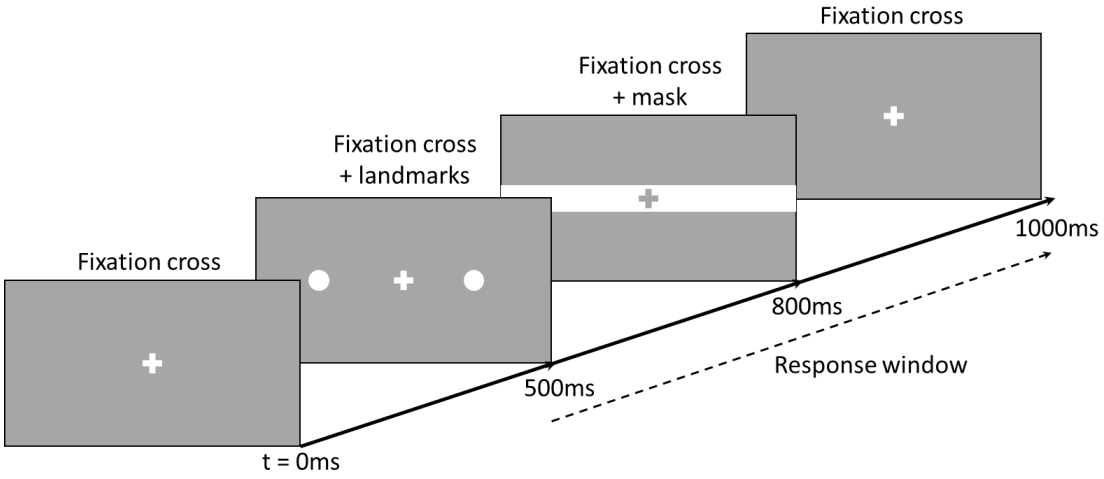

Figure 2. The time course of a single trial in the Landmark task.

Participants are instructed to indicate whether the left or the right landmark was closer to the fixation cross. They give their responses by pressing the green ("left") or red ("right") button (using the index and middle finger of the unaffected hand). The button press ends the trial and initiates the next trial. To control for response bias, in a separate, second block of the task, they are instructed to indicate which target was further away from the fixation cross by pressing the same buttons. The order of the two blocks is counterbalanced between participants. Attention bias is calculated from a relative number of "Left" and "Right" responses to each stimulus pair (landmarks position relative to the fixation cross). This is re-expressed in terms of affected versus unaffected sides of space and converted to a Point of Subjective Equality (PSE) using a cumulative Gaussian fit. The PSE expresses the relative distance at which the landmark on the

affected side of space should be further from (negative PSE values) or closer to (positive PSE values) the fixation cross for the two landmarks to be perceived as appearing at equal distance from the fixation cross. A negative PSE value indicates an attention bias away from the affected side and / or under-representation of that side of space. For example, if a participant with a left-affected limb indicates that the left landmark is appearing closer to the fixation cross more often than the right landmark (i.e., underestimating distance on left side), their PSE value will be negative and indicate reduced attention to or under-representation of the left (affected) side. We will average the PSEs from the two response blocks (which landmark was closer or further away from the fixation cross) to obtain a single spatial bias index for our analyses.

2.5.3.3.1.3. The Greyscales task

The Greyscales task is a sensitive measure of overt spatial attention bias. The task used in the present study follows a previously developed procedure [55]. Forty pairs of short (9.95° x 1.95°) and long (12° x 1.95°) greyscale bars (Figure 3) are presented in the centre of a white screen in a free-viewing condition until the response is given. Participants indicate if the top or the bottom bar appears overall darker by pressing the upper or lower button, respectively (using the index and middle fingers of their unaffected hand). The trials are separated by an 18° x 8° mask (random dot 1111 x 362 black and white pixel pattern of static) displayed for 150ms, after which the next trial begins. An attention bias score is calculated by subtracting the number of "rightward" responses (choosing whichever bar is darker on its right side, regardless of its vertical position) from the number of "leftward" responses and dividing the difference by a total number of trials. Negative scores indicate rightward bias, i.e. reduced attention to the left side. This will be re-expressed as bias relative to the affected / unaffected side.

Figure 3. Example pair of stimuli in the Greyscales task. A person who has reduced attention to the left side of space would judge the upper bar as having overall greater average darkness.

2.5.3.3.2. Mental representation of space

The Mental Number Line Bisection task aims to measure spatial bias in the mental representation of space. This is based on the evidence that people implicitly represent numbers in a linear

arrangement in which smaller numbers are located to the left side of space, and larger numbers are located to the right side of space [97]. The procedure is adapted from a previous study [56] in which pairs of numbers were read aloud to the participants and they were required to indicate the number that would fall midway between the two without making any calculations. The current task uses the same intervals (9, 16, 25, 36, 49 and 64) between two numbers that ranged from 2 to 98. For example, the midpoint number between 54 and 70 (16-interval) would be 62 (Figure 4). The only deviation from the previous procedure [56] is that every pair of numbers is presented twice – once in ascending and once in descending order, to reduce response bias. There are 84 trials presented in pseudorandom order and participants' verbal responses are inputted to the computer via the keyboard by the researcher. We subtract the subjective midpoint number from the objective midpoint number in each trial (for example, see Figure 4), and the average score is transformed to indicate the relative bias in the mental representation of space away (negative values) or towards (positive values) the affected hand-side. A bias away from the affected side was previously found in CRPS patients on Mental Number Line Bisection [56], as well as a rightward bias in post-stroke hemispatial (left) neglect patients [81, 98–100], and a leftward bias in healthy participants ("pseudoneglect") [56, 101, 102].

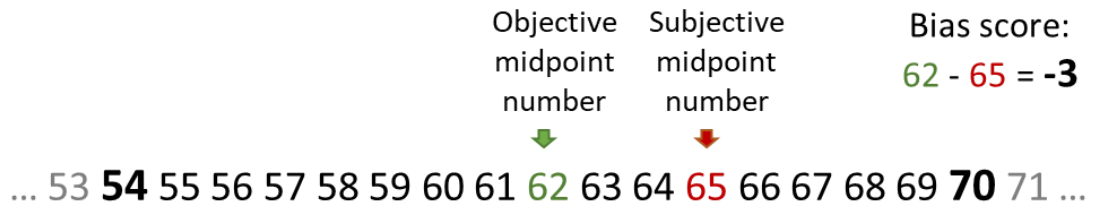

Figure 4. A pictorial representation of a theoretical trial from the Mental Number Line Bisection task. The participant is asked to indicate the midpoint number between the numbers 54 and 70, which are verbally presented by the experimenter. A negative bias score indicates that the centre of the participant's mental number line is shifted towards larger numbers, consistent with an under-representation of the left side of space relative to the right side of space.

2.5.3.3.3. Spatially-defined motor function

We use the Directional Hypokinesia task to assess two distinct forms of motor neglect – directional hypokinesia, i.e. relative slowing in the initiation of movements directed toward the affected side, and directional bradykinesia, i.e. relative slowing in the execution of movements directed toward the affected side of space [103]. The task measures movement initiation and execution times to targets that appear on the left or the right side of the screen. The task follows the exact procedure previously used for research with hemispatial neglect patients [57]. A black 1.4° fixation cross and two black 3° x 3° squares, one 12° to the left and one 12° to the right of the fixation cross, are on constant display (locations are re-expressed as affected and unaffected Visual Field, VF). Each trial is initiated by the participant pressing and holding a button with their index finger. After a time interval that varies randomly between 1500ms and 3000ms a black

target (1.4° high "X") appears inside one of the squares, in a pseudorandomized order, for 2000ms. The target onset initiates the response window and the participant is required to release the button, touch the screen in the location where the target appeared, and then return their index finger to the button as fast as possible, which initiates the next trial. There are 30 trials per block. A touch screen is used to monitor the accuracy of pointing-to-target movements. The Reaction Times (RTs) to release the button after the target onset (Movement Initiation Time, MIT) are recorded, as well as time taken between releasing the button and touching the screen (Movement Execution Time, MET). There are three different hand Starting Positions (location of the button box): 25cm to the left from body midline, central (aligned with the body midline), and 25cm to the right from body midline (the locations are re-expressed as the affected, central, and unaffected side). Manipulating the hand Starting Position allows dissociation between perceptual component of the task (e.g., slower detection of the targets on the affected side) and the true directional hypokinesia. Participants perform each condition once with each hand in separate blocks, giving a total of 6 conditions (unaffected hand from the unaffected side, unaffected hand from the centre, unaffected hand from the affected side, affected hand from the unaffected side, affected hand from the centre, affected hand from the affected side). The order of the Starting Positions is counterbalanced between participants, with the only restriction that they alternate between the unaffected and the affected hand in each subsequent block to reduce fatigue.

We will calculate mean MITs and METs for each combination of VF in which the target appeared (affected and unaffected) and hand Starting Position (affected, central, and unaffected location), separately for each hand used to complete the task. Directional hypokinesia would be indicated by slower initiation of movements (MIT) towards the affected side of space, independent of which arm is used [57, 103, 104]. Directional bradykinesia would be indicated by slower movement execution times (MET) towards targets appearing in their affected side of space, even when using the unaffected arm.

To dissociate any signs of directional hypokinesia from potential mechanical constraints, two indices of directional hypokinesia will be derived based on the analyses described in previous research [57]. Movement pathways and indices are illustrated in Figure 5. The first index (A) quantifies the difference in MITs to the targets in the affected vs. unaffected VF as a function of the direction of the movements [i.e. reaching toward the affected side (from central Starting Position) relative to reaching toward the unaffected side (from affected Starting Position). Index A will be calculated as: [central Starting Position (MIT affected VF – MIT unaffected VF) – affected Starting Position (MIT affected VF – MIT unaffected VF)]. Thus, a larger value on this index will indicate greater directional hypokinesia. A potential drawback of Index A is that it involves planning a movement across body midline (from the affected Starting Position to the unaffected VF) that covers a longer distance and may be more difficult than other movement trajectories. Therefore, we will also derive a second index (B) that directly quantifies the relative

slowing in the ability to initiate movements to the targets in the affected VF when making movements of the same physical length toward the affected side (from central Starting Position), versus toward the unaffected side (from affected Starting Position). Index B will be calculated as [central Starting Position (MIT affected VF) – affected Starting Position (MIT affected VF)]. Positive values on each index (A and B) would indicate hypokinesia for the affected side. Analogous indices A and B will be calculated for METs, and positive values of each index would indicate directional bradykinesia for the affected side.

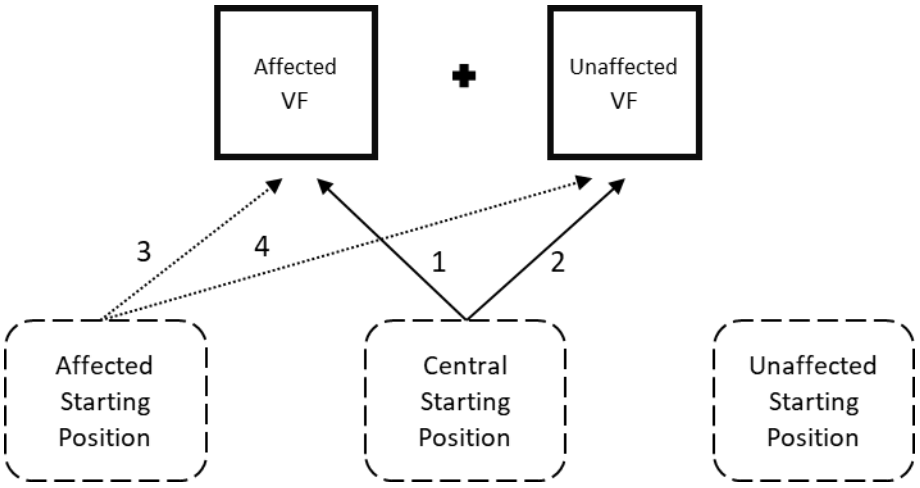

Figure 5. Indices of the Directional Hypokinesia task. Target locations (affected and unaffected Visual Field, VF) and hand Starting Positions (affected, central, and unaffected) are presented as an example of a participant with CRPS of left arm. Index A is calculated as initiation time of the movements represented by arrows [(1 – 2) – (3 – 4)]. Index B is calculated as initiation time of movements (1 – 3).

2.5.3.3.4. Body representation

As an objective measure of body representation, we use a modified Hand Laterality Recognition task based on a procedure described elsewhere [58]. The stimulus set was developed specifically for the current study (examples shown in Figure 6) and the final images were chosen based on the results of a pilot study reported in Additional file 2. The images depict gender-neutral right and left (mirror-reversed) hands in different postures and are presented at four different orientations (0°, 90°, 180° and 270°). In each trail, a black 0.1° fixation cross on a white background is on constant display. After 1000ms a colour image of a hand (12.9° x 12.9°) is randomly presented 8° to the left or to the right of the fixation cross (i.e., in the left or the right VF, as in a previously published similar procedure [8]) for 180ms. This period is short enough to prevent foveation of the stimuli, ensuring that the images are presented to one visual hemifield. The participants are required to indicate whether the image represented the right or the left hand by pressing the red or green button using the index and middle fingers of their unaffected hand. Speed and accuracy are both emphasised but there is no upper time limit for the response, and the button press initiates the next trial. Prior to the main task, participants complete a practice block of 12 trials (with

2000ms stimulus presentation times) that includes feedback, until they reach at least 75% accuracy across the entire practice block. They repeat the practice to ensure that they are able to perform the task above chance level. In the main task, there is a total of 100 trials (25 images x 2 hemifields x 2 depicted hands) conducted in a single block. Accuracy rates and RTs of the correct responses are calculated separately for the images of hands corresponding to the participant's affected and unaffected limbs, and for the VFs corresponding to their affected and unaffected side of space (matched sides in healthy controls). As the task requires mental rotation of the images of hands, slower RTs and lower accuracy rates are considered to be an indicator of a distorted representation of the depicted limb [8, 58, 105]. To obtain single Hand Laterality Recognition indices, we will also calculate the differences in accuracy rates and RTs between depicted affected and unaffected hands. Positive accuracy index (unaffected – affected) and positive RT index (affected – unaffected) would indicate distorted representation of the affected limb.

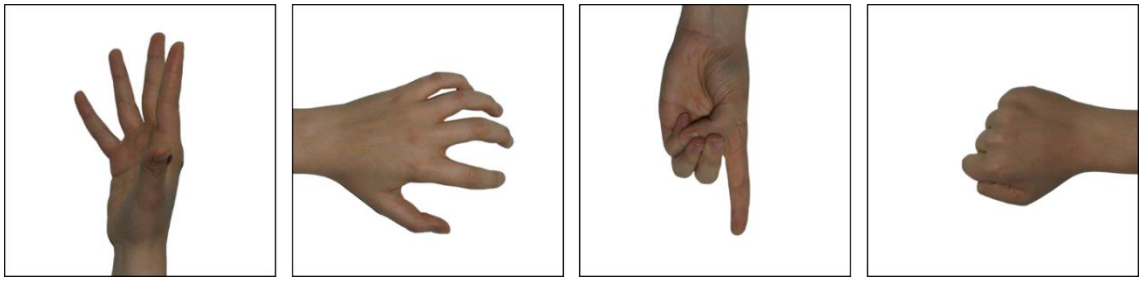

Figure 6. Example stimuli in the Hand Laterality Recognition task. Images of hands in four postures and rotation angles were included in the task.

2.6. Blinding

All outcome measurements are recorded by a researcher who is blind to group allocations (MH). A researcher (JHB) who is not involved in data collection allocates participants with CRPS to treatment groups 1-5 days before RS2. JHB or another researcher not involved in data collection (ADV) trains the participants in how to carry out the PA treatment or sham treatment in a self-guided manner at the end of RS2. The participants return the goggles in sealed opaque bags after completing the treatment in RS3 so that the primary researcher (MH) remains blind to their treatment allocation. MH will be unblinded as to the group allocations of the participants once the last person has completed RS4, as there will be no further research sessions in which she will assess symptoms. Follow-up measurements in weeks 19 (LTFU1) and 31 (LTFU2) will be carried out via postal questionnaires scored by research assistants who are blind to the group allocations.

The participants will be blind to their group allocations as they are not made aware of the specific nature of the intervention beyond that it involves sensory-motor coordination, nor the type of goggles used in the other treatment arm. In the information sheet and the training materials, the same terms are used to describe both treatment arms. For instance, all participants will be informed that sensory-motor training involves reaching out to targets with their affected arm while

wearing glasses fitted with lenses that distort vision. For ethical reasons, participants have to be told that they might receive either real or control treatment, and the meaning of double-blind randomized control trial will be explained to them in the information sheet and during training in how to carry out the treatment. A more general term "sensory-motor adaptation" is used to refer to PA in all study documents and instructions that the participants receive, to reduce the possibility that they could determine their treatment condition based on descriptions of PA on the Internet. At the end of the last in-person session (RS4) they will also be asked whether they have a belief about which condition they were allocated to, and their degree of confidence about this belief. They will be unblinded once data collection for this study is completed for all participants. Also, a participant might be unblinded before this time should they experience any worsening of symptoms that causes them concerns. If so, that participant will be withdrawn from the study in that no further data will be collected from them.

2.7. Statistical analyses

To process and analyse the data we will use IBM SPSS Statistics [106], R [107], and MATLAB [108] software. Hypotheses will be tested using a significance level of $\alpha = .05$. We will control type I errors in the primary analyses using Holm-Bonferroni corrections for multiple comparisons within each outcome analysis. No correction for multiple testing will be made in the exploratory analyses. We will report 95% bias-corrected and accelerated (BCa) bootstrap confidence intervals around all mean values.

Outliers are defined as scores outside ±3 SDs from the participant's mean score for a task condition (participant-level data) or from the group mean (group-level data) for a particular test or task condition. We will examine participant-level and group-level RT data in the Hand Laterality Recognition and Directional Hypokinesia tasks for the presence of outliers and use nearest neighbour replacement if any are identified. We will use the same method of nearest neighbour replacement for the group-level outliers identified on the remaining outcome measures.

T-tests and ANOVAS will be conducted to compare mean values between groups and between data collection time points. Statistically significant interactions will be interrogated through follow-up contrasts. Wilcoxon signed-rank tests and Mann-Whitney U tests will be used if assumptions of t-tests are violated; however, ANOVAs are robust to moderate violations of normality and homogeneity of variance. Therefore, we will use ANOVAs unless severe violations of normality, homogeneity of variance, and sphericity assumptions are present, in which case we will use linear mixed models analyses with bootstrapping procedures.

2.7.1. Sample size and power calculation

The required sample size was calculated based on the primary outcome measure of self-reported pain [109]. A meta-analysis defined a clinically significant reduction in pain as a change of $\Delta = -2$ (on a scale of 0-10) [110]. The sample size required to detect a pain reduction of this magnitude

between RS2 and RS3 was estimated. The risk of type I error was set at 5% and the risk of type II error was set at 10%, giving 90% power to detect a significant change in the pain. The standard deviation expected in the current study was estimated as 1.98 based on pain intensity ratings obtained by our group in recent research [9]. Given these parameters, a minimum of 42 participants with CRPS (21 per group) is required to evaluate the effects of the PA treatment on the primary outcome measure of pain. Taking into account an anticipated drop-out rate of 20%, up to 52 participants with CRPS will be enrolled in order to obtain a total of at least 21 complete datasets for RS1-RS4 per treatment group. To provide normative data, 21 healthy (pain-free) control participants will be recruited.

2.7.2. Timing

No interim analyses are planned. The timing of the final analyses will be stratified by planned length of follow-up for the relevant outcome measures. Once all participants have completed RS4, we will analyse the RS1-RS4 data to address our research questions regarding the efficacy of PA treatment in reducing CRPS symptom severity (RQ1) and the relationships between the severity of clinical symptoms of CRPS and neuropsychological changes in perception of and attention to the affected limb and its corresponding side of space in RS1 (RQ5). We will conduct separate analyses of current self-reported pain intensity, the BPI, the Pain Detect Questionnaire, the BPDS, the Tampa Scale for Kinesiophobia, the Profile of Mood States, and the Patient's Global Impression of Change scores once all participants meet the secondary endpoint (LTFU2).

2.7.3. Treatment outcome analyses

We will conduct intention to treat (ITT) as our primary analysis to examine the overall effects of prism adaptation. The ITT analysis will include all participants with CRPS who were allocated to either treatment arm, regardless of their treatment adherence and completion of outcome measurements. ITT analysis is the recommended approach to evaluating treatment outcomes in randomized trials because it minimizes potential selection bias related to the fact that outcome data is rarely missing completely at random (e.g. loss to follow-up might be related to a patient's response to treatment) [111]. To account for missing data from participants who withdraw from the trial after treatment allocation, their baseline post-randomisation observation (RS2) will be carried forward as a conservative estimation of their outcomes in ITT analysis, as the participants are expected to return to pre-treatment baseline over time. The exception is the Patient Global Impression of Change questionnaire that is only completed in the post-treatment research sessions, in which case the RS3 observation will be carried forward, if available. Missing data from the computer-based tasks within each research session will be replaced by group mean for the particular task condition (with an exception of Directional Hypokinesia task, where some participant with CRPS may not be able to complete the task using the affected limb; in such cases

only the conditions completed with the unaffected limb will be analysed). Missing daily logbook ratings will be interpolated using linear regression.

The ITT analysis is a relatively conservative approach, which might underestimate potential treatment benefit [111]. Therefore, we will also conduct a supportive per-protocol (PP) analysis, also known as complete case analysis, to see whether PA treatment can benefit the participants with CRPS who were able to perform it according to the trained protocol compared to those participants who were able to complete the sham treatment according to trained protocol [112]. The PP population will be the subset of the ITT population who provided complete outcome data for RS1-RS4 (i.e. attended all in-person research sessions and completed the primary outcome measures) and missed no more than 6 treatment sessions.

We will use confidence intervals to compare the RS1 primary outcomes scores of the participants with CRPS who withdrew and those who remained in the trial until RS4 to assess any potential selection bias. The flow of participants, including timing and reasons for withdrawal, as well as number of participants included in the ITT and PP analyses of each primary outcome, will be presented in a CONSORT diagram.

2.7.4. Descriptive characteristics

We will report baseline characteristics for individual participants with CRPS such as affected limb, type of inciting injury, CRPS duration, co-morbidities, prescribed medications and other treatments, and change in handedness score.

Minimisation factors listed in Table 2 will be presented as group means for continuous factors or proportion of participants in each group who are classed positive on each categorical factor. We will conduct a series of contrasts and chi-square tests to confirm that the minimisation procedure successfully equated the two groups on these factors. Contrasts will also be used to confirm that the PA and sham treatment groups are matched on mean Profile of Mood States, Tampa Scale for Kinesiophobia, Revised Life Orientation Test, and Patient Centred Outcomes Questionnaire scores.

2.7.5. Efficacy of PA treatment in reducing pain and CRPS symptom severity (RQ1)

A 2x6 ANOVA with Group as a between-subjects factor (PA treatment, sham treatment), and Time (RS1, RS2, RS3, RS4, LTFU1, LTFU2) as a within-subject factor will be conducted for the first primary outcome of pain intensity rating. We will also conduct sixteen *a-priori* contrasts to compare RS1 vs. RS2, RS2 vs. RS3, RS3 vs. RS4, RS2 vs. RS4, RS2 vs. LTFU1, RS4 vs. LTFU1, LTFU1 vs. LTFU2, and RS2 vs. LTFU2 within each group. We will also conduct a 2x4 ANOVA with the factors Group (PA treatment, sham treatment) and Time (RS1, RS2, RS3, RS4) for the second primary outcome of CPRS severity score, followed by eight *a-priori* contrasts comparing RS1 vs. RS2, RS2 vs. RS3, RS3 vs. RS4, and RS2 vs. RS4 within each group. We are primarily

interested in detecting any changes between RS2 and RS3 which would represent immediate effects of treatment.

Minimisation factors (see Table 2) may be included as covariates in the ANOVAs if there are significant differences at RS1. Similarly, if we find significant group differences in the Profile of Mood States, Tampa Scale for Kinesiophobia, or Revised Life Orientation Test RS1 scores, these variables may be used as covariates in the ANOVAs on pain and CRPS severity score.

We will also calculate the Number Needed to Treat (NNT) separately for pain and CRPS severity score. The NNT will be based on the proportion of participants in each treatment arm that achieved clinically significant pain relief (≥2 points on 0-10 NRS scale [110]) and reduction in CRPS symptom severity (≥4.9 points [35]) in RS3 compared to RS2.

2.7.6. Effects of PA treatment on neuropsychological changes and other secondary outcomes (RQ2) and time course of any improvements (RQ3)

To analyse between-group (PA treatment vs. sham treatment) differences on the secondary outcome measures (see Table 3) across four (RS1-RS4) or six (RS1-LTFU2) time points, we will conduct 2x4 or 2x6 ANOVAs as described for the analyses of the primary outcomes. Specifically, a 2x4 ANOVA will be run on each clinical assessment outcome (limb temperature asymmetry, hands size difference, grip strength and ΔFTP ratios, MDT, MPT, two-point discrimination threshold ratios, and allodynia) and mean group scores in the following computer-based measures: PSSs in the TOJ task, PSEs in the Landmark task, attention bias scores in the Greyscales task, and bias scores in the MNLB task. We will also use 2x4 ANOVAS to analyse between-group differences on indices A and B for the affected and unaffected hand performance in the Directional Hypokinesia task, as well as on hand laterality recognition accuracy and RTs indices in the Hand Laterality Recognition task across RS1-RS4. Separate 2x6 ANOVAs will be run on mean group scores on each of the self-reported questionnaire measures: pain intensity and interference components of the BPI, the Pain Detect Questionnaire, The BPDS, the Tampa Scale for Kinesiophobia, and the Profile of Mood States.

We will plot group means of daily ratings of average pain, range of movement, and interference over time and use contrasts to identify the time points of significant group differences. We will also identify for both groups and for each measure the average number of days to reach peak improvement from the start of treatment, and the average number of days from the peak improvement to return to baseline.

2.7.7. Predictors of the response to PA treatment and / or CRPS progression over time (RQ4)

We will conduct exploratory analyses of the potential factors that can predict response to treatment for the PA group. First, we will calculate reduction scores as a change in current pain

scores and CRPS severity scores from the immediate pre-treatment to immediate post-treatment sessions (RS3 – RS2). Second, we will conduct two separate linear mixed models regressions on pain reduction scores and CRPS severity reduction scores including the pertinent explanatory factors such as demographic characteristics; current pain intensity; CRPS severity score; and scores on the self-report questionnaires, clinical assessments, and computer-based tests. In the first instance, we will consider those outcomes that differed the most from the healthy control participants in RS1 (see statistical analyses for RQ5 in the next section).

The same factors will be considered potential explanatory variables in linear mixed models regressions on current pain scores and CRPS severity scores across four research sessions (RS1-RS4). These exploratory analyses will be conducted for data from all the participants with CRPS to examine possible predictors of CRPS progression over time (including but not limited to treatment group).

2.7.8. Baseline neuropsychological symptoms and their relationships with the clinical symptoms of CRPS (RQ5)

We will conduct a series of contrasts to compare mean age, proportion of males and females, and proportion of left- and right-handed individuals between participants with CRPS in RS1 (total CRPS sample, regardless of subsequent treatment allocation) and healthy controls. Participants' mean scores on self-report questionnaires and clinical assessments in RS1 will also be compared between the two groups. Specifically, we will conduct contrasts to compare participants with CRPS and healthy controls groups on the BPDS and Profile Of Mood States scores; the hand laterality indices (current for healthy controls, and handedness before CRPS for the participants with CRPS); limb temperature asymmetry and hands size difference (affected – unaffected), grip strength and ΔFTP ratios (affected / unaffected), MDT, MPT, two-point discrimination threshold ratios, and mean allodynia score on the affected side.

To test whether the participants with CRPS in RS1 show visuospatial attention bias compared to healthy controls, we will use four separate contrasts. Specifically, we will conduct four between-group comparisons of the following variables: PSSs in the TOJ task, PSEs in the Landmark task, attention bias scores in the Greyscales task, and bias scores in the MNLB task.

The Directional Hypokinesia task conditions performed with the affected and unaffected hand will be analyzed separately. After excluding incorrect and missed trials, we will use mean movement initiation times (MITs) and movement execution times (METs) for each combination of VF in which the target appeared and hand Starting Position to test if the participants with CRPS show signs of directional hypokinesia compared to the healthy controls. We will conduct two three-way ANOVAs on MITs for each hand with the following factors: Group (participants with CRPS, healthy controls), VF (affected, unaffected), and Starting Position (affected, central, unaffected). Significant interactions will be followed by four *a-priori* contrasts to test whether the

participants with CRPS are slower to initiate movements toward the targets in their affected side of space (regardless of the direction of reaching movement required) and / or in the direction toward their affected side of space (regardless of the location of the target). Specifically, we will examine if participants with CRPS have slower MITs to the targets in the affected VF than in the unaffected VF; to the affected VF compared to healthy controls; to the affected VF from central compared to affected Starting Position; and to the affected VF from central Starting Position compared to healthy controls. Analogous analyses will be conducted on METs to test if participants with CRPS show signs of directional bradykinesia compared to healthy controls. We will also examine differences between Groups (participants with CRPS, healthy controls) on MITs and METs through separate contrasts for each index (A and B) of directional hypokinesia and bradykinesia. As further exploratory analyses we will examine how many participants with CRPS are impaired on both indices (A and B) of directional hypokinesia and bradykinesia by identifying which participants obtained positive A and B indices and by comparing each CPRS patient's indices to the mean indices for healthy controls using Crawford t-tests [113].

To test for differences in body representation as measured by the Hand Laterality Recognition task between the participants with CRPS and healthy controls, we will conduct two three-way ANOVAS with the factors Group (participants with CRPS, healthy controls), depicted Hand (affected, unaffected), and VF (affected, unaffected) on accuracy rates and RTs to accurate responses. If there are significant three-way interactions, we will conduct *a-priori* contrasts to test whether the participants with CRPS are less accurate and / or slower in responding to: the depicted hands corresponding to their affected hand compared to those corresponding to their unaffected hand when the hands are presented in the affected VF; the affected hands presented in the affected VF compared to the unaffected VF; the affected hands compared to the unaffected hands; the affected hands presented in the affected VF compared to healthy controls; the affected hands compared to healthy controls; and the hands presented in the affected VF compared to healthy controls. If there is no effect of VF, we will only consider accuracy rates / RTs to recognize affected and unaffected hands averaged across both VFs in follow-up contrasts and any further correlation / regression analyses.

2.7.8.1. Relationships between neuropsychological changes and clinical symptoms of CRPS

Correlation and regression analyses will be conducted to test relationships between neuropsychological changes (as measured by computer-based tasks) and clinical symptoms of CRPS (as measured by self-report questionnaires and clinical assessments). These analyses will depend on which outcomes show significant differences between participants with CRPS and healthy controls, thus they are exploratory.

3. Discussion

Considering the poor overall response to conventional medical treatments for CRPS [114], it is important to seek novel methods of pain relief and symptoms improvement. PA is an emerging treatment that targets spatial attention deficits, has shown early promise as an intervention for CRPS, and might operate through different mechanisms to mirror visual feedback (another neurocognitive treatment for CRPS [23, 115]).

The ongoing trial that is described in this protocol is the first to investigate the effects of PA treatment on pain and CRPS symptom severity using a double-blind, randomized, and sham-controlled design in a patient sample that is large enough to detect a clinically significant reduction in pain. These aspects of our design, as well as stratified randomisation and intention to treat and per-protocol analyses will allow unbiased evaluation of a brief, low-cost treatment that can be easily self-administered by the participant in a home setting.

However, self-guided administration of the treatment might also be its limitation in the resent study, as it prevents us from directly monitoring participants' compliance. This is considered a necessary trade-off to test the treatment as it would be most likely integrated into CRPS management. Furthermore, opting for home-based treatment will aid the recruitment of a sufficient number of participants, who are drawn from a broad geographical area, as it would not be feasible for them to travel to the research centre for each treatment session, or for another researcher to repeatedly assess their compliance. We put in place several measures to encourage adherence to treatment, such as in-person training, instructions and guidance in multiple media, and easy access to advice. To avoid adding another layer of difficulty and increasing potential burden of treatment (especially for those participants who do not have very good technical competence), we decided against asking participants to video-record their treatment sessions. Thus, we rely solely on self-reported adherence, that is, recording the timing and completion of each treatment session in daily logbooks. This could limit the interpretation of our findings; however, we will evaluate them considering the possibility that participants may have not complied with the treatment regimen as expected.

While clearly defining our primary outcome measures, the trial includes a wide range of secondary outcome measures to assess the impact of treatment on pain and other clinical CRPS symptoms, as well as neuropsychological and emotional functioning, and symptoms' interference with daily life. These measures will allow us to explore relationships between self-reported, clinical, and neuropsychological manifestations of CRPS from baseline data, independent of the primary research aim of testing the efficacy of PA.

Despite their informative value, large number of secondary outcomes might reduce the quality of data. To mitigate the potential impact of long duration and burden of research sessions, we composed a battery of assessments that would take no longer than four hours to complete,

including breaks between assessments. We also provide the participants with overnight accommodation near the research centre in cases when long travels are required, to minimise their fatigue during research sessions. In light of how little is known about cognitive changes in CRPS and effects of PA on these changes, broad battery of neuropsychological tests seems appropriate.

Furthermore, this research may identify potential individual differences accounting for the course of CRPS and response to treatment. The findings could provide an indication of how to identify the patients who are most likely to benefit from PA based on their cognitive and physical symptoms. This would inform subsequent research and therapies.

If PA brings benefits beyond that of the sham treatment on the primary outcome measures of the ongoing trial, this treatment should be developed as a recommended method to reduce pain and other CRPS symptoms. The study is likely to expand on our limited understanding of this debilitating condition and its neuropsychological components.

4. List of abbreviations

BPDS: Bath CRPS Body Perception Disturbance Scale; BPI: Brief Pain Inventory; CRPS: Complex Regional Pain Syndrome; FTP: Finger-To-Palm distance; LTFU1: Long Term Follow-Up 1 (week 19) by post; LTFU2: Long Term Follow-Up 2 (week 31) by post; MDT: Mechanical Detection Threshold; MET: Movement Execution Time; MIT: Movement Initiation Time; MPT: Mechanical Pain Threshold; NRS: Numerical Rating Scale; PA: Prism Adaptation; PSE: Point of Subjective Equality; PSS: Point of Subjective Simultaneity; RS1: Research Session 1 (week 1); RS2: Research Session 2 (week 4); RS3: Research Session 3 (week 7); RS4: Research Session 4 (week 11); RSDSA: Reflex Sympathetic Dystrophy Syndrome Association; RT: Reaction Time; QST: Quantitative Sensory Testing; TOJ: Temporal Order Judgement; VF; Visual Field.

5. Declarations

5.1. Ethics approval and consent to participate

This trial gained approval from National Health Service Oxfordshire Research Ethics Committee A and Health Research Authority, reference number 12/sc/0557, and from the University of Bath Psychology Ethics Committee (16-333). Major protocol amendments are implemented only after formal approval from the Research Ethics Committee. Any protocol updates are also documented and dated on the ISRCTN trial record. The researcher who is responsible for data collection (MH) obtains informed consent from each participant that is signed and dated prior to any study-related procedures. Verbal consent to continue with the study is taken at the beginning of each consecutive research session. Participants can withdraw from the trial at any time. The study sponsor, the University of Bath, is involved in the trial management through providing data storage and ethical supervision (Contact: Prof. Jonathan Knight, pro-vc-research@bath.ac.uk, Claverton Down Road, Bath BA2 7AY, UK).

5.2. Consent for publication

Not applicable.

5.3. Availability of data and material

There is no data associated with the current paper, which describes a protocol for a clinical trial that is in progress at the time of submission. All investigators will have access to the final dataset. Anonymised participant-level data from the trial will be stored using the Open Science Framework repository and access will be granted upon request. Access shall be requested by contacting the corresponding author via email. Description of the data and specific instructions for gaining access will be listed in a publicly available format in the repository. The data will be made available in this format at the time that the paper describing the trial outcome is published, upon MH's graduation from her PhD, or two years after the end of data collection (whichever comes first). Obtained results will be communicated to participants, clinicians, and the public through newsletters, talks and press releases.

Materials that were modified or developed specifically for the purpose of the current trial, as well as data management plan, will be available from the project's webpage at Open Science Framework upon completion of data collection for the trial.

5.4. Competing interests

The authors declare that they have no competing interests.

5.5. Funding

The study is funded by Reflex Sympathetic Dystrophy Syndrome Association (RSDSA). The RSDSA approved the design of the study and have no other role regarding the use of the data or preparation of the manuscript.

5.6. Authors' contributions

The study was conceived of by JHB. JHB, MH, ADV and MJP contributed to design. JHB and MJP secured the funding. MH developed the testing protocols, programmed the computer-based tasks, and prepared the draft. MH and JHB devised the randomisation with minimisation procedure. All the authors have read and approved this version of the manuscript.

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Chapter 3 – Conclusions

The design of this double-blind, randomised, controlled trial meets the gold standard of clinical research for evaluating the effectiveness of interventions. Prospective trial registration (ISRCTN46828292) and submission of the trial protocol and analysis plan for publication prior to any data analyses facilitate unbiased evaluation of outcomes. The major advantage of this trial compared to previous studies of prism adaptation treatment for CRPS is that it includes a control treatment that will allow me to dissociate any effects of prism adaptation treatment from other non-specific effects, such as placebo or mere increased movement of the affected limb. It also employs blinding of participants and the researcher, which minimizes the effects of expectations and biased assessment and reporting of treatment outcomes. Moreover, the CRPS PRISMA trial is sufficiently powered to detect a clinically significant reduction in the primary outcome of pain intensity. Although it is not specifically powered to detect a significant change in the second primary outcome of CRPS symptom severity score, this relatively new measure has not been previously used in any interventional studies. Therefore, the results of this pioneer trial could contribute important information, such as effects size of any treatment-related change in CRPS severity score, which would be useful for planning future clinical trials. The CRPS PRISMA trial tracks the long-term progression of clinical manifestations of CRPS, patients' psychological functioning, and performance on the neuropsychological tests over 2.5 to 7.5 months. This expands on the longitudinal case study described in Chapter 2 by assessing any fluctuations in neuropsychological symptoms in a large representative group of people with CRPS. In fact, this trial recruits one of the largest CRPS samples that has been thus far involved in experimental research.

Notwithstanding the abovementioned significant contributions to the field of CRPS research, the design of the trial has its limitations. One potential issue is related to the randomisation procedure, which is restricted by minimisation of baseline group differences according to a considerable number of participant characteristics. However, in contrast to traditional stratification approach, minimisation ensures good balance between groups even when several factors are considered (Altman & Bland, 2005). Furthermore, the primary objective of randomisation is to ensure equal representation of any factors other than active treatment component in two groups, so that any difference in outcomes can be attributed to the effect of treatment. Yet this assumption is rarely realistic in practice when simple randomisation is used, especially in heterogeneous samples such as people with CRPS. Therefore, to ensure balance of potential confounders between groups, minimisation has been suggested as the platinum standard of allocation techniques in clinical trials (Treasure & MacRae, 1998). As discussed in this chapter, the main potential limitation of the trial design is monitoring participants' compliance with treatment regimen based solely on self-reported completion of each treatment session. This is, however, a necessary trade-off to accommodate pragmatic considerations (i.e. the lack of resources to monitor every treatment

session), as well as the likely way that the treatment would be applied if it was incorporated into CRPS management. Following the chronological order in which the data were collected, I will first present the baseline performance of participants with CRPS compared to healthy controls on experimental tests of spatial cognition and spatially-defined motor function, and explore the relationships between the severity of clinical and neuropsychological symptoms (Chapter 4). This will provide context for interpreting the findings related to treatment outcomes (Chapter 5).

Chapter 4: Disputing space-based biases in unilateral Complex Regional Pain Syndrome

Chapter 4 – Introduction

In Chapter 1, I reviewed the existing (often contrasting) evidence of a range of neuropsychological symptoms found in people with CRPS. I concluded that there appears to be substantial heterogeneity regarding intact and impaired cognitive functions, and that we need large, controlled studies, using sensitive tests, to characterise the nature and prevalence of any deviations. Furthermore, Chapter 2 provided proof of concept that people with CRPS can present with spatial biases beyond any response biases or primary sensory deficits, and that we can quantify them using sensitive psychophysical tasks. In this chapter, I will use similar experimental methods to investigate any deviations in perceptual, representational, and motor aspects of spatial cognition in a relatively large cohort of people with CRPS, compared to a group of pain-free controls. The CRPS sample size in this study is considered large relative to previous experimental studies on spatial biases in CRPS, which recruited two-to-five times smaller samples, and relative to pragmatic consideration of the difficulty to recruit participants with this rare chronic disease. Although I summarised evidence for changes to a broad range of neuropsychological functions in Chapter 1, this study specifically focuses on changes in spatial cognition and motor control that resemble those typical of hemispatial neglect after brain injury. These neuropsychological symptoms are particularly relevant for prism adaptation treatment, which I will assess in Chapter 5.

This chapter will address the question of whether people with CRPS show systematic "neglect-like" symptoms, and what domains of spatial cognition and / or motor function are affected. Previous research suggested that people with CRPS tend to pay less attention to information in the affected side of space rather than on the affected limb itself (Bultitude et al., 2017; Moseley et al., 2009; Moseley, Gallace, & Iannetti, 2012; Reid et al., 2016). The case study in Chapter 2 further indicated that spatial biases might be independent of body representation. Thus, in the present study, I aim to obtain a measure of lateralised visual biases in near space without potential confounding of body-related information that could be introduced by, for example, tests of attention to tactile stimuli. To assure that any effects are not task-specific, for instance, related to temporal acuity or demands of fast processing speed, I will administer three visual tests of different aspects of spatial cognition: covert and overt visual spatial attention, and the visual representation of space. Furthermore, I will assess two other "neglect-like" symptoms that have not been extensively studied in CRPS before: biases in mental representation of space using mental number line bisection, and directional aspect of motor neglect using a spatially-defined motor function task. This battery of neuropsychological tasks will allow a systematic assessment of multiple domains of spatial cognition to identify any significant areas of dysfunction.

This chapter will also address the question of the clinical relevance of neuropsychological symptoms in CRPS. Investigating the relationships between spatial cognition and clinical manifestations of CRPS has two potential implications. First, it could help to account for the heterogeneity across groups of individuals with CRPS, both in terms of clinical and neuropsychological presentations. Second, it might allow researchers and clinicians to identify individuals who would be most likely to benefit from neurocognitive rehabilitation. As I discussed in Chapter 1, the evidence of clinical relevance of neuropsychological changes is mixed. Recognizing the multifactorial mechanisms of CRPS, in this study, I will take an exploratory approach to consider a wide range of possible predictors of two key clinical outcomes: pain intensity and CRPS symptom severity. These predictors include self-report measures of psychological functioning, objective assessments of sensory, autonomic, and motor function, and experimental tests of spatial cognition. I will additionally explore the potential clinical and psychological predictors of biases in spatial cognition to provide preliminary evidence of what might be driving any neuropsychological changes.

While a number of studies reported "neglect-like" symptoms in people with CRPS, based on self-report and experimental measures, there is also emerging evidence contradicting these findings. Furthermore, we currently lack a complete understanding of the nature and clinical relevance of these neuropsychological symptoms, yet they already formed the basis of new rehabilitation approaches. In order to maximise the effectiveness of such treatments, we must understand the extent of neuropsychological changes in CRPS and evaluate their relation to clinical signs of the disorder. This chapter will contribute to this knowledge and provide a basis for interpreting the effects of prism adaptation on clinical symptoms and neuropsychological functions in CRPS, which I will present in Chapter 5.

Statement of authorship

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Candidate's contribution to the paper (provide details, and also indicate as a percentage)	Monika Halicka considerably contributed to this study (80%), being involved in formulation of ideas (65%), design of methodology (70%), experimental work (100%), and presentation of data in journal format (95%).		
Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.		
Signed	Monika Halicka	**Date**	10.05.2020

Chapter 4

Disputing space-based biases in unilateral complex regional pain syndrome

Monika Halicka[a,b]*, Axel D Vittersø[a,b,c], Hayley McCullough[d], Andreas Goebel[d,e], Leila Heelas[f], Michael J Proulx[b,g], Janet H Bultitude[a,b]

[a]Centre for Pain Research, University of Bath, Claverton Down Road, Bath, BA2 7AY, UK
[b]Department of Psychology, University of Bath, Claverton Down Road, Bath, BA2 7AY, UK
[c]Department of Sport and Health Sciences, University of Exeter, Magdalen Road, Exeter, EX2 4TA, UK
[d]Pain Research Institute, Department of Translational Medicine, University of Liverpool, Lower Lane, Liverpool, L9 7AL, UK
[e]Department of Pain Medicine, Walton Centre NHS Foundation Trust, Lower Lane, Liverpool, L9 7AL, UK
[f]Optimise Pain Rehabilitation Unit, Oxford University Hospitals NHS Trust, Windmill Road, Oxford, OX3 7HE, UK
[g]Centre for Reality & Virtual Environments Augmentation Labs, Department of Computer Science, University of Bath, Claverton Down Road, Bath, BA2 7AY, UK

*Corresponding author:

Monika Halicka
mon.halicka@gmail.com
Department of Psychology
University of Bath
Claverton Down Road
Bath BA2 7AY
United Kingdom

Declaration of interest:

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Abstract

There is some evidence that people with Complex Regional Pain Syndrome (CRPS) show reduced attention to the affected relative to unaffected limb and its surrounding space, resembling hemispatial neglect after brain injury. These neuropsychological symptoms could be related to central mechanisms of pathological pain and contribute to its clinical manifestation. However, the existing evidence of changes in spatial cognition is limited and often inconsistent. We examined visuospatial attention, the mental representation of space, and spatially-defined motor function in 54 people with unilateral upper-limb CRPS and 22 pain-free controls. Contrary to our hypotheses and previous evidence, individuals with CRPS did not show any systematic spatial biases in visuospatial attention to or representation of the side of space corresponding to their affected limb (relative to the unaffected side). We found very little evidence of directional slowing of movements towards the affected relative to unaffected side that would be consistent with motor neglect. People with CRPS were, however, slower than controls to initiate and execute movements with both their affected and unaffected hands, which might suggest disrupted central motor networks or overall psychomotor slowing. Finally, we found no evidence of any clinical relevance of changes in spatial cognition because there were no relationships between the magnitude of spatial biases and the severity of pain or other CRPS symptoms. The results did reveal potential relationships between CRPS pain and symptom severity, subjective body perception disturbance, and extent of motor impairment, which would support treatments focused on normalizing body representation and improving motor function. Our findings suggest that previously reported spatial biases in CRPS might have been overstated.

Keywords

Complex Regional Pain Syndrome; neuropsychological symptoms; spatial cognition; motor function; body representation

Abbreviations

BPDS = Bath CRPS Body Perception Disturbance Scale; BPI = Brief Pain Inventory; CRPS = Complex Regional Pain Syndrome; EHI = Edinburgh Handedness Inventory; MNLB = Mental Number Line Bisection; POMS = Profile of Mood States; PSE = Point of Subjective Equality; PSS = Point of Subjective Simultaneity; TOJ = Temporal Order Judgement; VF = Visual Field.

1. Introduction

Growing evidence supports the notion that chronic pain is a disease of the central nervous system involving functional and structural reorganisation of the brain (for reviews, see Henry, Chiodo, & Yang, 2011; Lee, Nassikas, & Clauw, 2011; Seifert & Maihöfner, 2008). One condition in which such reorganisation has been observed is Complex Regional Pain Syndrome (CRPS), a disorder that can affect one or more limb(s) and involves pain and other sensory, motor, and autonomic symptoms that are disproportionate to any inciting injury. Abnormal higher-order cortical processing in CRPS is further evidenced by cognitive changes in the representation of and attention to the CRPS-affected limb and the corresponding side of external space (e.g. Bultitude, Walker, & Spence, 2017; Legrain, Bultitude, De Paepe, & Rossetti, 2012; Lewis, Kersten, McCabe, McPherson, & Blake, 2007; Moseley, Gallace, & Spence, 2009; Schwoebel, Coslett, Bradt, Friedman, & Dileo, 2002). These changes have been referred to as "neglect-like" because they resemble those typical of hemispatial neglect that can occur after brain injury. For example, deficits in attention to or representation of the affected (relative to unaffected) side have been found on tests of tactile attention (Moseley et al., 2009, 2012; Reid et al., 2016), visual attention (Bultitude et al., 2017; Filbrich et al., 2017), and the mental representation of space (Sumitani et al., 2014). Furthermore, similar to people with hemispatial neglect after brain injury, people with CRPS reported or presented with underutilisation of the affected limb during spontaneous movements that could not be fully explained by primary motor deficits (Galer et al., 1995; Galer & Jensen, 1999). Systematic measurement of motor performance of people with CRPS revealed slower and more variable movements when they used their affected hand, but also when movements were performed in the affected side of space regardless of which hand they used (Reid et al., 2018). Thus, there is evidence that people with CRPS can show space-based neuropsychological changes that resemble perceptual, representational, and motor neglect.

Previous studies suggest that there is a relationship between spatial biases and the manifestation and maintenance of CRPS symptoms. For example, the severity of self-reported "neglect-like" symptoms (Frettlöh et al., 2006) was associated with greater pain intensity, worse long-term pain outcomes, sensory loss, and motor impairment in the affected limb (Frettlöh et al., 2006; Kolb et al., 2012; Wittayer et al., 2018). Also, the magnitude of perceptual and motor spatial biases on experimental tasks correlated with greater pain intensity and longer CRPS duration (Reid et al., 2016, 2018). Furthermore, larger temperature asymmetry between the affected and unaffected arms was related to greater magnitude of tactile spatial attention bias (Moseley et al., 2009, 2012). This asymmetry was reduced by resting the affected hand in the unaffected side of space, and by using prismatic lenses to produce the illusion of such positioning (Moseley et al., 2012, 2013). Reduction of pain and other CRPS symptoms following prism adaptation treatment (Bultitude & Rafal, 2010; Christophe, Chabanat, et al., 2016; Sumitani, Rossetti, et al., 2007), which is thought to increase attention to the affected side relative to the unaffected side, further supports the clinical

relevance of spatial attention in CPRS. Therefore, understanding spatial biases in CRPS, and how they relate to clinical symptoms, could provide insights into the prevention and treatment of the disorder.

Some findings, however, have called into question the presence of spatial biases in CRPS, or the extent to which they resemble hemispatial neglect. There is a share of research showing no evidence of spatial biases in CRPS (e.g. Christophe, Chabanat, et al., 2016; Filbrich et al., 2017; Filippopulos, Grafenstein, Straube, & Eggert, 2015; Förderreuther, Sailer, & Straube, 2004; Kolb et al., 2012; Reid et al., 2016; Reinersmann et al., 2012; Wittayer et al., 2018). Furthermore, some researchers found that people with CRPS presented with spatial biases in the *opposite* direction to what would be considered "neglect-like". The best example of such findings is that the representation of external space relative to one's body was shifted towards the CRPS-affected side in several group studies (Sumitani et al., 2014; Sumitani, Rossetti, et al., 2007; Sumitani, Shibata, et al., 2007; Uematsu et al., 2009). Two case reports also described a CRPS patient who consistently showed higher attention to her affected side relative to her unaffected side across a battery of tests of spatial cognition (Christophe, Delporte, et al., 2016; Jacquin-Courtois et al., 2017). Some of these negative findings could be due to insufficient sensitivity of the tests used. For example, subtle spatial biases in people with CRPS, who typically do not have any brain injury, might not be evident on tasks such as classic pen-and-paper line bisection. Small sample sizes, in combination with the known heterogeneity of CRPS presentation (Bruehl et al., 2016; Marinus et al., 2011), could also account for some of the inconsistencies between studies regarding the observed presence or direction of spatial biases. Furthermore, very few previous studies tested different aspects of neglect (i.e. perceptual, representational, and motor) in the same group of participants (see Christophe, Chabanat, et al., 2016; Reid et al., 2016; Sumitani et al., 2014 for exceptions). Therefore, it can be difficult to ascertain if discrepancies between the demonstrated spatial biases (or lack thereof) across studies are due to differences between the participants, or because CRPS can affect one aspect of spatial cognition and not another. The aim of the present study was therefore to use sensitive measures to examine multiple aspects of spatial cognition in a large sample of individuals with CRPS.

We designed a battery of tests based on established approaches used to measure hemispatial neglect following a stroke, as well as pseudoneglect (the mild leftward bias that is commonly found in groups of healthy participants when performing certain spatial tasks; Jewell & McCourt, 2000). We used three experimental tasks to test for visuospatial biases. The first, the Temporal Order Judgement (TOJ) task, requires participants to indicate the relative timings of pairs of spatial stimuli (one presented in each visual field). The TOJ measures covert spatial attention, based on the premise that information that is subject to greater attention is perceived earlier relative to information that is subject to lesser attention (Spence & Parise, 2010). The second, the Landmark task, requires participants to judge the relative distance of two stimuli and is thought

to measure visuospatial representations (Makin et al., 2010). A tendency to underestimate the distance on one side of space (relative to the other) would be consistent with diminished visual representation of that side. The third, the Greyscales task (Nicholls et al., 1999), requires participants to judge the relative luminance of two equally shaded greyscale stimuli that are arranged one above the other such that one stimulus has greater luminance on the left and one has greater luminance on the right. Participants with an attention bias will tend to show greater reliance on the luminance difference on one side of the stimulus display when making their decision. This tests for any bias in overt spatial attention without posing temporal demands on the task. In addition to the tests of visuospatial biases, our battery also included a Mental Number Line Bisection (MNLB) task designed to measure any biases in mental representations of space. This is based on the existing evidence that numbers are mentally represented in a linear arrangement (with smaller numbers located to the left, and larger numbers to the right side of space; Dehaene, Bossini, & Giraux, 1993). Thus, individuals with biased mental representation of space will tend to underestimate or overestimate the midpoint of number intervals on a mental number line. Finally, to test for any spatial biases in motor function, we measured the speed of movement initiation and execution when participants reached from different starting locations towards targets appearing either in the affected or unaffected side of space. Slower initiation of movements directed towards the affected relative to unaffected side of space, even with the unaffected hand, defines directional hypokinesia towards the affected side, whereas slower execution of the same movements defines directional bradykinesia. This test of spatially-defined motor function was identical to that used previously to measure directional hypokinesia in right-hemisphere stroke patients (Sapir et al., 2007). We hypothesised that participants with CRPS (compared to pain-free controls) would present with spatial biases in attention to and representations of the affected side of space, and with slowed initiation and execution of movements directed towards the affected relative to unaffected side of space.

In addition to evaluating group differences in spatial cognition, we also explored relationships between pain, CRPS severity, and the extent of any neuropsychological changes in people with CRPS. Previously discussed literature shows that changes in spatial cognition correlate with clinical features of CRPS such as pain intensity, sensory and motor impairment, and temperature asymmetry (Frettlöh et al., 2006; Kolb et al., 2012; Moseley et al., 2009, 2012, 2013; Reid et al., 2016, 2018; Wittayer et al., 2018). There is also evidence to suggest that they are associated with other cognitive abnormalities (e.g. body perception disturbance; Bultitude et al., 2017) and psychological distress (e.g. depression, anxiety; Michal et al., 2016; Wittayer et al., 2018). However, the relationships between spatial biases and clinical CRPS symptoms are not consistently found (Bultitude et al., 2017; Filbrich et al., 2017; Frettlöh et al., 2006; Michal et al., 2016; Reid et al., 2016; Reinersmann et al., 2012; Vittersø et al., 2020). Considering that some potentially relevant outcomes might be overlooked in the existing literature, we explored our data for relationships between spatial biases and a broad range of participant characteristics (such as

age, CRPS duration, and change in hand preference), clinical outcomes (sensory, motor, and autonomic function), self-reported pain, and psychological factors (body perception disturbance, pain-related fear of movement, and mood disturbance). We hypothesised that the magnitude of any observed neuropsychological symptoms would be related to the severity of clinical signs of CRPS.

2. Methods

This study involved a single study visit that was a part of a randomised controlled trial to evaluate the effects of prism adaptation on pain and severity of CRPS symptoms (CRPS PRISMA Trial, ISRCTN46828292; see Halicka et al., 2020 for the trial protocol; Chapter 3). The same participants also completed a hand laterality recognition task, which will be reported elsewhere as this was designed to measure lateralised body representation distortion rather than spatial cognition per se. The data reported in this article were collected prior to any trial-related intervention. During the single study visit, participants completed self-report questionnaires; underwent assessment of sensory, motor, and autonomic function; and completed experimental tests of neuropsychological function. The study visit lasted between two to four hours, including breaks between the assessments. The results of the randomised controlled trial will be reported elsewhere. All procedures were carried out in accordance with the Declaration of Helsinki and received ethical approval from National Health Service Oxfordshire Research Ethics Committee A (ref. 12/sc/0557).

Participants were recruited through the National CRPS-UK Registry, internal registry of the Walton Centre NHS Foundation Trust, Oxford University Hospitals NHS Foundation Trust, and other NHS clinics in the UK, word of mouth, advertisements on the funder's and research centre's websites, and social media. Participants were screened for eligibility through a telephone interview. To obtain a sample size meeting the trial requirements (21 patients completing the trial for each of the two treatment groups; Halicka et al., 2020; Chapter 3), we enrolled 54 adults with CRPS-I affecting primarily one upper limb for at least three months, who met the Budapest research diagnostic criteria at the time of testing (Harden et al., 2010). The control sample consisted of 22 adults without current or chronic pain, who were matched to 22 individual participants with CRPS (i.e. size of one treatment group) by sex, self-reported handedness, and age (±5 years). One limb of each control participant was labelled as the "matched" (i.e. "affected") limb according to the affected limb of their matched participant with CRPS. Note that although sample sizes are imbalanced, we would expect more variability in the heterogeneous (but larger) sample of participants with CRPS than in healthy control participants (Rusticus & Lovato, 2014). All participants enrolled in the study had no history of neurological disorders, no severe psychiatric disorders that might be associated with perceptual changes (e.g. schizophrenia), were not legally blind, and had sufficient English language ability to provide informed consent.

Participants completed their study visit at the Universities of Bath (36 participants with CRPS, all controls), Liverpool (10 participants with CRPS), or at participants' homes if unable to travel (8 participants with CRPS).

2.1. Questionnaire measures

All participants completed the Edinburgh Handedness Inventory (EHI; Oldfield, 1971) on which negative scores (< -40) indicate left-handedness and positive scores (> 40), right-handedness. Mood can affect the pain experience (e.g. Tang et al., 2008) and performance on attentional tasks (e.g. Moriya & Nittono, 2011). Therefore, all participants also completed the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1971). The Bath CRPS Body Perception Disturbance Scale (BPDS; Lewis & McCabe, 2010) was used to assess subjective cognitive representation of the CRPS-affected / matched limb. This was completed by all participants because it is a non-validated scale with no normative data currently available. Participants with CRPS answered additional questionnaires that were not completed by the control participants. They answered the EHI a second time to rate their *recalled* handedness prior to the onset of CRPS symptoms. An absolute difference between the current and recalled handedness scores (ΔEHI) was calculated to approximate the functional impact of the disorder. Pain severity and interference were assessed using a short form of the Brief Pain Inventory (BPI; Cleeland, 1996) and the neuropathic component of pain was measured using the Pain Detect Questionnaire (Freynhagen et al., 2006). Participants with CRPS also completed the Tampa Scale for Kinesiophobia (Miller et al., 1991), which measures pain-related fear of movement and re-injury. Higher scores on the abovementioned questionnaires indicate greater mood disturbance (POMS), more severe distortion of body representation (BPDS), greater pain severity and interference (BPI), greater neuropathic component of pain (Pain Detect), and more severe kinesiophobia (Tampa Scale).

2.2. Sensory, motor, and autonomic function

We used a validated protocol to confirm that participants met the CRPS research diagnostic criteria, to quantify CRPS severity (Harden et al., 2017), and to confirm that the control participants did not present with signs or symptoms of CRPS on their matched limb. We objectively quantified the CRPS signs described below. Temperature asymmetry was quantified as a difference between an average of three hand temperature measurements on the unaffected and affected side (in the centre of the most painful site, and on the dorsal and palmar hand surface over the thenar muscle) using an infrared thermometer (Duratool, thermal resolution 0.1°C). We quantified oedema as a difference between an average of three hands size measurements on the affected and unaffected side using the figure-of-eight procedure (Pellecchia, 2003) with a soft tape measure (cm). Weakness was quantified as a ratio of grip strength in the affected to the unaffected hand, measured as an average of three maximum strength grips of an electronic dynamometer with each hand (kg force; Constant, model 14192-709E). We quantified active

range of movement as a ratio of delta finger-to-palm distance (cm; delta refers to the difference between full extension and full flexion of fingers; Torok et al., 2010) in the affected hand to the unaffected hand.

Hypoesthesia, hyperalgesia, and allodynia were additionally quantified using elements of a standardized Quantitative Sensory Testing protocol (Rolke et al., 2006), administered to the centre of most painful region on the affected / matched limb and the corresponding site on the unaffected limb. Mechanical Detection Thresholds were assessed with von Frey filaments (0.008-300g force; Bioseb, model Bio-VF-M). A positive ratio of thresholds for affected vs. unaffected side indicates hypoesthesia (i.e. increased tactile detection threshold) on the affected limb. We used pinprick stimulators (8mN-512mN; MRC Systems Pin Prick Stimulator Set) to quantify Mechanical Pain Thresholds. A positive thresholds ratio for affected vs. unaffected side indicates hyperalgesia (i.e. decreased pain threshold) on the affected limb. Allodynia was assessed by applying with a single sweeping motion a cotton ball, Q-tip, and a brush to the skin, five times each in a random order. Allodynia was quantified as an arithmetic mean of 15 ratings for each sensation from 0 ("no pain, no sharp, pricking, stinging, or burning sensation") to 100 ("most intense pain sensation imaginable") on the affected limb. This procedure was adapted from the Dynamical Mechanical Allodynia test (Rolke et al., 2006). We also examined tactile discrimination thresholds on index fingertips of each hand using a Two-Point Discriminator disk (Exacta, North Coast Medical; Pleger et al., 2006). Using a staircase procedure, the participant's finger was touched with either one tip or two tips of the disk, starting with two points separated by 7mm distance and then increasing or decreasing the distance (down to a single tip) across trials depending on participant's responses (i.e. whether they reported feeling one or two tips, respectively). The thresholds were calculated as a geometric mean of five subthreshold and five suprathreshold values. A positive thresholds ratio for the affected vs. unaffected side indicates decreased precision of tactile discrimination ability of the affected limb.

2.3. Experimental tests of neuropsychological changes

Participants completed three experimental tests of visuospatial attention (the TOJ, Landmark, and Greyscales tasks; see Figure 1a-c), one test of the mental representation of space (the MNLB task; see Figure 1d), and one test of spatially-defined motor function (see Figure 3). For convenience, these tasks were completed in the following order: the Landmark task, the Greyscales task, the test of spatially-defined motor function, the TOJ task, and the MNLB. All tasks except the MNLB were administered via PsychoPy software (Peirce, 2007) using a touch-screen laptop computer (Windows 10 operating system, screen dimensions 34.5cm x 19.4cm, resolution 1920 x 1080 pixels). For the tests of visuospatial attention and spatially-defined motor function, the participant's head was stabilised by a chinrest aligned with a central fixation and positioned at 50cm distance from the screen. Note that the TOJ stimuli were not presented on the computer screen (see section 2.3.2.1.), but participants did use the chinrest. Key-press and key-release

responses were recorded using a custom-made button-box. The button-box was aligned with the centre of the screen for all tasks, except for specific blocks of the test of spatially-defined motor function in which it was also placed to the left or right of the screen (see section 2.3.4.). Participants used their unaffected hand to press the buttons in the Landmark and Greyscales tasks, and both hands (one at the time per block) in the test of spatially-defined motor function. When manual responses were not required (i.e. in the TOJ and MNLB tasks), participants rested their uncrossed hands in their lap under the table.

The data from the computer tasks were transformed to reflect the participants' performance relative to their affected / unaffected side of the body or visual field. For example, participants with CRPS whose right limb was affected would have their responses to left-sided stimuli coded as "unaffected side", and responses to right-sided stimuli as "affected side" (and vice versa for participants whose left limb was affected). To enable comparison of both groups relative to affected and unaffected side, control participants' limbs were coded as "affected" and "unaffected" with respect to their matched participant with CRPS (regardless of the participants' handedness).

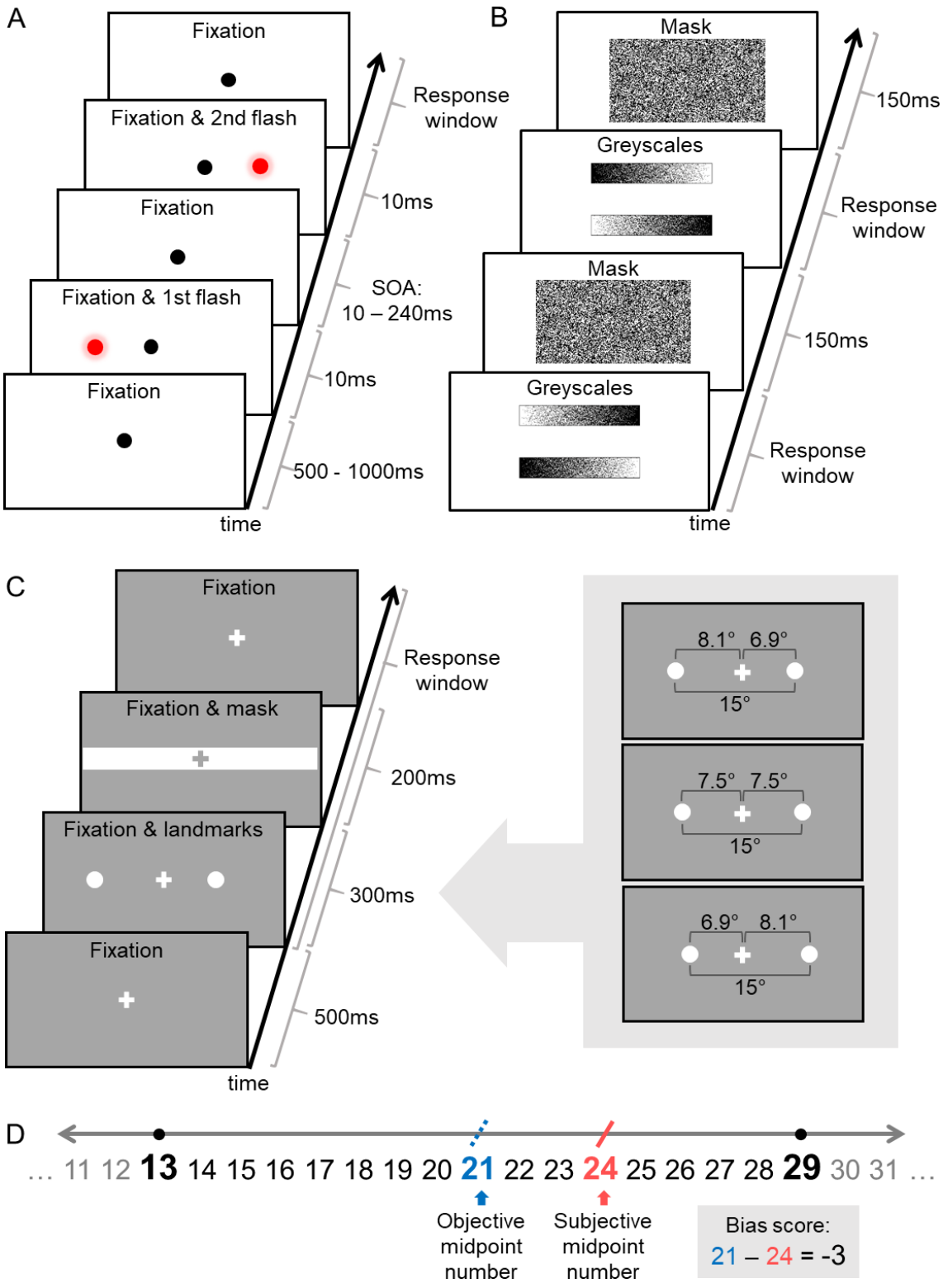

Figure 1. Experimental tests of visuospatial attention (A-C) and the mental representation of space (D). Text within the illustrated screenshots did not appear during the study and is for illustration purposes only. (A) In the Temporal Order Judgement (TOJ) task, the participant maintained their gaze on the central fixation point and verbally reported which light flash ("left" or "right") appeared first or second, depending on the response block. In each trial, the two lights were presented onto a white table surface with one of ten possible Stimulus Onset Asynchronies (SOAs). (B) In the Greyscales task, the stimuli were on constant display until the participant pressed a button to indicate which of the two greyscale bars (upper or lower) appeared overall

darker. Then the stimuli were replaced by a mask, and the next trial began. (C) In the Landmark task, the participant maintained their gaze on the fixation cross and pressed a button to indicate which landmark (left or right) appeared further from or closer to the fixation cross, depending on the response block. The right inset panel illustrates three out of 13 possible arrangements of the landmark stimuli (lines and numbers are for illustration purposes only). The top rectangle corresponds to the left landmark being furthest from, and the right landmark being closest to fixation; the middle rectangle corresponds to both landmarks being equidistant from fixation; and the bottom rectangle corresponds to the left landmark being closest to, and the right landmark begin furthest from fixation. The distance between the two landmarks was constant (15°), while their relative horizontal distance from fixation varied by 0.1° across trials. In each trial, the landmarks were replaced by a mask after 300ms. (D) In the Mental Number Line Bisection task, the experimenter presented each trial verbally, e.g. "What is the midpoint number between 13 and 29?". The participant verbally reported their subjective midpoint number (e.g. "24") without making any calculations. Deviation from the objective midpoint (e.g. "21") on each trial was calculated by subtracting the subjective midpoint from the objective midpoint. In all four tasks, participant's non-speeded response initiated the next trial.

2.3.2. Visuospatial attention

2.3.2.1. The Temporal Order Judgement (TOJ) task

For the TOJ task, participants verbally reported the order of two brief (10ms) identical lights that were projected onto a white table surface using laser pointers controlled via an Arduino platform. The lights appeared one 9cm to the left and one 9cm to the right of a central fixation point located approximately 28cm away from participant's torso. Pairs of lights were presented 15 times for each of the ten temporal offsets (±10, ±30, ±60, ±120 and ±240ms; negative values represent the trials in which the left light appeared first) in pseudorandom order, resulting in 150 trials (Figure 1a). To account for potential response biases (Filbrich et al., 2016), participants completed the TOJ task twice: once indicating which light appeared first, and once indicating which light appeared second (block order was counterbalanced). For each block, the relative number of participant's "right light appeared first" or "left light appeared second" responses to the range of temporal offsets was fitted with a cumulative Gaussian using a criterion of maximum likelihood to obtain the Point of Subjective Simultaneity (PSS). Following the transformation from left / right to affected / unaffected, the PSS values were averaged between the two response blocks to give a single value for each participant. The PSS is an index of spatial attention bias and indicates the amount of time (ms) by which the light on the affected side must precede (negative PSS) or follow (positive PSS) the light on the unaffected side for the two stimuli to be perceived as simultaneous. Therefore, negative PSS values indicate reduced attention to the affected relative to the unaffected side and positive numbers indicate greater attention to the affected relative to the unaffected side.

2.3.2.2. The Landmark task

We designed a version of the Landmark task based on one previously used to demonstrate underrepresentation of the side of near space corresponding to the missing limb in amputees

(Makin et al., 2010). In each trial, two identical landmarks (white circles) were simultaneously presented on a computer screen with a fixed distance between them (15°), but in different positions relative to central fixation. The stimulus locations varied from ±8.1° to ±6.9° away from fixation in the horizontal plane by 0.1° increments (e.g. -8.1° and +6.9°, -8.0° and +7.0°, -7.9° and +7.1°, etc., up to -6.9° and +8.1°; see Figure 1c for example stimulus pairs). Negative values represent the location of the left landmark, and positive values the location of the right landmark, with reference to central fixation at 0°. Each pair of landmarks was presented 15 times in each of 13 possible arrangements (including equidistant), resulting in 195 trials. Similar to the TOJ task, participants completed the Landmark task twice to account for any response biases: once indicating which landmark appeared further from fixation, and once indicating which landmark appeared closer to fixation (block order was counterbalanced). For each block, the relative number of participant's keypress responses to the range of spatial offsets indicating "right landmark appeared further" or "left landmark appeared closer" was fitted with a cumulative Gaussian to derive the Point of Subjective Equality (PSE). Following the transformation from left / right to affected / unaffected, the PSE values were averaged between the two response blocks to give a single value for each participant. The PSE is an index of spatial bias that represents the relative distance (°) at which the landmark on the affected side should be further from (negative PSE) or closer to (positive PSE) central fixation for the two landmarks to be perceived as equidistant. Therefore, negative PSE values indicate under-representation of the affected side of space relative to the unaffected side and positive values indicate over-representation of the affected side of space relative to the unaffected side.

2.3.2.3. The Greyscales task

In each trial of the Greyscales task (Nicholls et al., 1999), participants were presented with two vertically aligned greyscale bars that were positioned one on top of the other. Each bar was darker at one end than the other, and the two bars were mirror images of each other such that one was darker on the left and the other was darker on the right even though both bars had the same average luminance (Figure 1b). Participants indicated with a button press which bar (top or bottom) was darker overall (in free-viewing conditions). The number of times the participant chose a bar that was darker on its right side, regardless of its vertical position, was subtracted from the number of times the participant chose a bar that was darker on its left side. We then divided this value by total number of trials (i.e. 40) to calculate an index of spatial attention bias. Transformed negative scores indicate reduced attention to the affected side of space, consistent with making higher proportion of relative darkness judgements based on the side of the stimuli corresponding to the unaffected limb.

2.3.3. Mental representation of space

We used a Mental Number Line Bisection (MNLB) task based on that of Sumitani et al. (2014). In each trial, participants were instructed to verbally estimate, without calculating, the midpoint

number between a given pair of numbers (Figure 1d). There were 84 trials with pairs of numbers separated by intervals of 9, 16, 25, 39, 49, and 64 digits, with the individual numbers ranging from 2 to 98. Number pairs were read aloud by the researcher in pseudorandom order. To account for potential response bias, each numbers pair was presented once in ascending (e.g., 54 and 70) and once in descending (e.g., 70 and 54) order. Individual spatial bias scores were computed by subtracting participant's subjective midpoint number from the objective midpoint number in each trial and averaging the results across trials. A negative index indicates a relative bias towards guessing larger numbers as the midpoint number. That is, following the transformation from left (smaller numbers) / right (larger numbers) to affected / unaffected, a negative index indicates a bias away from the affected side of the mental representation of space.

2.3.4. Spatially-defined motor function

We adapted a test for directional hypokinesia previously used in research on hemispatial neglect (Sapir et al., 2007) to test for spatially-defined (directional) motor deficits in CRPS patients. Each trial was initiated by the participant holding down a button with an index finger, while maintaining their gaze on a central fixation cross flanked by two squares located 12° to the left (left Visual Field, VF) and 12° to the right (right VF) from fixation (see the inset panel in Figure 3). After a time interval that randomly varied between 1500ms and 3000ms, a target ("X") appeared in one of the squares for 2000ms. The target location was pseudorandomized across 30 trials within each block and expressed relative to the CRPS-affected / matched side (i.e. in terms of the affected and unaffected VFs rather than left and right VFs). Participants were instructed to make speeded movements to release the button and touch the target location on the touch-screen using the same finger, and then return their hand to hold down the button, which initiated the next trial. We recorded the reaction time to release the button after target onset (movement initiation time) and the time between releasing the button and touching the screen (movement execution time). There were three hand Starting Positions in which the button box was either aligned with the body midline or located 25cm to the left or to the right from the body midline. These locations were expressed relative to the CRPS-affected (or matched "affected") limb, that is, as the central, affected, and unaffected Starting Positions. Participants completed six blocks of the task in total: two blocks from each Starting Position (order counterbalanced), one with each Hand (alternating between the affected and unaffected hand between consecutive blocks). Slower initiation and execution of movements directed towards the affected side of space, independent of the hand used, would be taken to indicate directional hypokinesia and bradykinesia, respectively.

2.4. Data handling and statistical analyses

The data was processed and analysed using MATLAB 2018b, IBM SPSS Statistics 25, R 3.5.3, and JASP 0.9.2.0 software. The significance level for frequentist hypotheses testing was $\alpha = .05$. For Bayesian analyses we used the suggested cut-offs for Bayes factor (BF_{10}; Lee &

Wagenmakers, 2014). We used Holm-Bonferroni correction for multiple comparisons to control for family-wise type I error in the primary analyses. Corrections were not implemented in exploratory analyses.

Pre-processing of the data from the spatially-defined motor function task involved removing invalid trials from individual data sets, i.e. trials in which the screen touch did not match the target location or the button was released before target onset (for movement initiation time analysis), and additionally the trials in which screen touch time was not recorded (for movement execution time analysis). In total, 7.25% of all completed trials were removed across all participants. Outliers in participant-level data in this task were identified as scores outside ±3 *SDs* from the participant's score for a task condition and replaced with the nearest non-outlier values (0.84% of all valid data replaced). Missing questionnaire items in participant-level data were replaced with participant's mean rating for the specific subscale calculated without the missing items (person mean replacement; 0.08% of all questionnaire items replaced across all participants).

For group-level data, scores outside ±3 *SDs* from the group mean for each test or task condition were identified as outliers and replaced with the nearest non-outlier values. Missing data points on clinical measures and computer-based tasks were replaced with a group mean for particular test or task condition, with the exception of the test of spatially-defined motor function (six participants with CRPS could only complete the task using the unaffected limb, thus they were excluded from the affected limb analysis). In group-level data, 1.22% of all data points were replaced as missing or outlying values across all measures and all participants.

Bootstrapping was implemented for descriptive and inferential statistics using 1000 bootstrap samples and calculating bias corrected and accelerated 95% confidence intervals (BCa 95% CIs). For non-parametric tests, we used Monte Carlo estimation of 95% CIs based on 1000 samples. Between-group differences on categorical variables were estimated through chi-square statistics. To compare mean scores on the continuous variables between participants with CRPS and control participants, we conducted *t* tests and ANOVAs, and interrogated significant interactions through contrasts. Where assumptions of *t*-tests were violated, we carried out Wilcoxon signed-rank tests and Mann-Whitney *U* tests and reported median scores. Due to missing data and violations of normality, homogeneity of variance, and sphericity assumptions for ANOVAs in the data from the test of spatially-defined motor function, bootstrapped linear mixed models analyses were conducted instead to investigate the interactions of interest. To investigate any potential relationships between neuropsychological changes and clinical signs of CRPS in the data from participants with CRPS, we conducted exploratory best subsets regression analyses.

3. Results

3.1. Participant characteristics; questionnaire measures; and sensory, motor, and autonomic function

A small proportion of participants reported CRPS symptoms in body parts other than the primarily affected upper limb - most commonly the ipsilateral lower limb (7% of total sample), with single instances of contralateral lower limb (not meeting the CRPS diagnostic criteria), and both lower limbs. A quarter of the CRPS sample reported other, non-CRPS pain. In most cases it was fibromyalgia (13% of total sample), but there were also single instances of joint hypermobility; shoulder, hip, and back pain; migraine; hernia; peripheral neuropathy in the ipsilateral lower limb; and contralateral upper limb pain. The most common comorbidities other than pain included depression (35% of total sample), anxiety (20%), asthma (13%), hypertension (9%), polycystic ovaries (7%), diabetes, irritable bowel syndrome, and arthritis (6%). There were also single cases of hypothyroidism, tachycardia, endometriosis, psoriasis, contralateral carpal tunnel syndrome, epilepsy, anaemia, incontinence, Fowler's syndrome, and Crohn's disease. Ongoing treatments and medications for CRPS at the time of the study involved opioids (56%), anti-depressants (48%), anticonvulsants (46%), paracetamol (44%), physiotherapy and / or occupational therapy (39%), nonsteroidal anti-inflammatory drugs (33%), local anaesthetics (15%), other medication (6%), spinal cord stimulation (4%), and transcutaneous electrical nerve stimulation (4%).

Group-level participant characteristics are reported in Table 1, including average scores on the self-reported measures of pain, kinesiophobia, body perception disturbance, mood, and hand preference; and tests of sensory, motor, and autonomic function. Participants with CRPS and controls were equally matched on mean age, proportion of males and females, and proportion of left- and right-handed participants in each group ($ps > .05$).

Participants with CRPS reported moderate pain severity and interference on the BPI (Li et al., 2007) and their mean score on the Pain Detect Questionnaire ($\geq$ 19 cut-off) suggested a likely neuropathic pain component (Freynhagen et al., 2006). Despite comparable pain intensity, median CRPS severity score in our sample was higher than in a group of people with chronic (on average 35 months) CRPS tested in the severity score validation study (Harden et al., 2017). This could be because we only included people who met more stringent Budapest research (compared to clinical) diagnostic criteria. The mean score on the Tampa Scale for Kinesiophobia indicated high pain-related fear of movement, comparable with previous CRPS research (Velzen et al., 2019). BPDS scores of participants with CRPS were significantly higher compared to controls, indicating significantly distorted perception of the CRPS-affected limb. POMS scores were also significantly higher among participants with CRPS than controls, indicating greater mood disturbance. There was no difference between the median handedness index of the control participants and recalled (pre-CRPS) handedness of participants with CRPS. Sixty-nine percent

of those whose dominant arm was affected by CRPS, or who were ambidextrous before the symptoms onset, showed a change in hand preference towards the unaffected arm according to the absolute difference in the scores on the EHI answered with regard to current and pre-CRPS handedness.

Participants with CRPS presented with significantly larger asymmetries between the affected and unaffected limbs compared to controls in limb temperature (both signed and absolute difference), grip strength, finger-to-palm distance, and mechanical pain threshold (see Table 1). Specifically, the affected limb was on average characterised by lower temperature, weaker grip strength, more limited range of movement, and greater hyperalgesia. Participants with CRPS also had significantly more severe allodynia on the affected limb than the control participants. There were no significant between-group differences in oedema, mechanical detection thresholds, and two-point discrimination thresholds.

Table 1 *Group-level participant characteristics; scores on questionnaire measures; and quantification of sensory, motor, and autonomic function of the affected limb relative to the unaffected limb in participants with CRPS compared to healthy controls*

Measure	CRPS	Control	Contrast
Participant characteristics			
Age (years) *M*	45.94 [42.65, 49.28]	45.95 [40.23, 51.41]	$t(74) < 0.01$, $p = .998$, $d < 0.01$
Sex (% female)	85%	77%	$\chi^2(1) = .69$, $p = .406$, $\phi = 0.10$
Handedness (% right-dominant pre-CRPS)	93%	96%	$\chi^2(1) = .21$, $p = .648$, $\phi = -0.05$
Primarily affected / matched limb (% left)	59%	64%	$\chi^2(1) = .13$, $p = .723$, $\phi = 0.04$
CRPS in other body parts (%)	11%	N.A.	
Other non-CRPS pain (%)	26%	N.A.	
CRPS duration (months since diagnosis) *Mdn*	47.00 [37.00, 65.00]	N.A.	
Current pain intensity (0 – 10 NRS) *Mdn*	6.00 [6.00, 7.00]	N.A.	
CRPS severity score (/16) *Mdn*	12.50 [12.00, 13.00]	N.A.	
Self-report questionnaires			
BPI – Pain severity (/10) *M*	5.80 [5.34, 6.22]	N.A.	
BPI – Pain interference (/10) *M*	5.57 [4.96, 6.13]	N.A.	
Pain Detect Questionnaire (/38) *M*	24.13 [22.55, 25.63]	N.A.	
Tampa Scale for Kinesiophobia (/68) *M*	39.28 [36.79, 41.74]	N.A.	
BPDS (/57) *M* ***	28.20 [25.11, 31.31]	14.00 [11.55, 16.27]	$t(74) = -7.19$, $p < .001$, $d = -1.55$

Measure	CRPS	Control	Contrast
POMS (/200) *M* ***	88.54 [79.54, 97.96]	36.96 [32.19, 41.95]	$t(74) = -8.97$, $p < .001$, $d = -1.85$
EHI (-100 – 100; pre-CRPS) *Mdn*	100.00	83.00 [71.00, 100.00]	$U = 502.00$, $p = .300$, $d = 0.24$
Δ EHI (absolute change pre- to post-CRPS) *Mdn*	42.00 [20.00, 54.50]	N.A.	
Sensory, motor, and autonomic function			
Temperature asymmetry (°C)[a] *Mdn* ***	-0.42 [-0.77, -0.23]	0.02 [-0.15, 0.25]	$U = 286.50$, $p < .001$, $d = 0.88$
Absolute temperature asymmetry (°C) *Mdn* **	0.52 [0.30, 0.83]	0.23 [0.17, 0.33]	$U = 346.00$, $p = .002$, $d = 0.69$
Oedema (figure-of-eight; cm)[a] *M*	-0.02 [-0.30, 0.29]	-0.13 [-0.36, 0.11]	$t(74) = -0.44$, $p = .659$, $d = -0.12$
Grip strength (dynamometry; kg)[b] *Mdn* ***	0.35 [0.25, 0.39]	1.00 [0.99, 1.10]	$U = 57.00$, $p < .001$, $d = 1.99$
Range of movement (Δ Finger-To-Palm distance; cm)[b] *Mdn* ***	0.70 [0.62, 0.89]	1.00 [1.00, 1.00]	$U = 37.50$, $p < .001$, $d = 2.14$
Mechanical Detection Threshold (g force)[c] *Mdn*	-0.04 [-0.44, 0.21]	-0.01 [-0.24, 0.46]	$U = 548.00$, $p = .605$, $d = 0.12$
Mechanical Pain Threshold (mN)[d] *Mdn* **	0.58 [0.38, 0.67]	0.00 [-0.29, 0.13]	$U = 357.50$, $p = .005$, $d = 0.65$
Allodynia (0 – 100 NRS) *Mdn* ***	17.83 [9.53, 28.33]	0.00	$U = 87.00$, $p < .001$, $d = 1.79$
Two-Point Discrimination threshold (mm)[c] *M*	-0.06 [-0.19, 0.07]	-0.06 [-0.18, 0.07]	$t(74) = 0.02$, $p = .983$, $d < 0.01$

Note. **$p < .01$; ***$p < .001$. BPI = Brief pain inventory; BPDS = Bath CRPS Body Perception Disturbance Scale; POMS = Profile of Mood States; EHI = Edinburgh Handedness Inventory (score -100 indicates extreme left-handedness, and 100 extreme right-handedness). [BCa 95% CI].
[a]Side difference (affected – unaffected), where positive numbers indicate that the affected limb is warmer / larger; [b]Side ratio (affected / unaffected), where numbers < 1 indicate weakness / limited range of movement in the affected limb; [c]Side ratio [(affected - unaffected) / affected], where positive numbers indicate hypoesthesia / less precise tactile discrimination on the affected limb; [d]Side ratio: [(unaffected - affected) / unaffected], where positive numbers indicate hyperalgesia on the affected limb.

3.4. Experimental tests of neuropsychological changes

3.4.2. Visuospatial attention

Two-tailed contrasts showed that the performance of participants with CRPS on the three tasks measuring visuospatial attention did not significantly differ from the performance of healthy controls. Specifically, the PSS values in the visual TOJ task were not significantly different between the participants with CRPS (*Mdn* = -0.27; BCa 95% CI [-7.61, 3.97]) and controls (*Mdn* = -5.17, BCa 95% CI [-10.97, 0.27]), $U = 472.00$, $p = .152$, $d = 0.33$ (Figure 2a). Similarly, the PSEs of participants with CRPS in the Landmark task (*Mdn* = 0.05; BCa 95% CI [-0.04, 0.10]) did not significantly differ from the PSEs of the control participants (*Mdn* = 0.06, BCa 95% CI [-

0.15, 0.26]), U = 551.00, p = .624, d = 0.11 (Figure 2b). Finally, there were no between-group differences in the bias scores on the Greyscales task (CRPS: M = 0.11, BCa 95% CI [-0.02, 0.23]; controls: M = 0.01, BCa 95% CI [-0.17, 0.19]), $t(74)$ = -0.81, p = .422, d = -0.20; Figure 2c). Follow up Bayesian analyses using a Cauchy prior width of 0.707 indicated anecdotal evidence of no difference between groups for PSSs (BF_{10} = 0.44) and Greyscales bias scores (BF_{10} = 0.34), and moderate evidence of no difference between groups for PSEs (BF_{10} = 0.27) (Lee & Wagenmakers, 2014). CRPS participants' performance on the TOJ task did not correlate with the other visuospatial tasks, but there was a moderate positive relationship between their scores on the Greyscale and Landmark tasks (r = 0.40; see Figure S2).

3.4.3. Mental representation of space

MNLB bias scores of the participants with CRPS (M = 0.02, BCa 95% CI [-0.39, 0.43]) were not significantly different to those of the healthy controls (M = 0.09, BCa 95% CI [-0.52, 0.65]; $t(74)$ = 0.18, p = .860, d = 0.05; Figure 2d), suggesting unbiased mental representation of space. A Bayesian independent-samples t-test indicated moderate evidence of no difference (BF_{10} = 0.26). CRPS participants' performance on the MNLB task was moderately positively correlated with their performance on the Greyscales and Landmark tasks (r = 0.37 and 0.38; see Figure S2).

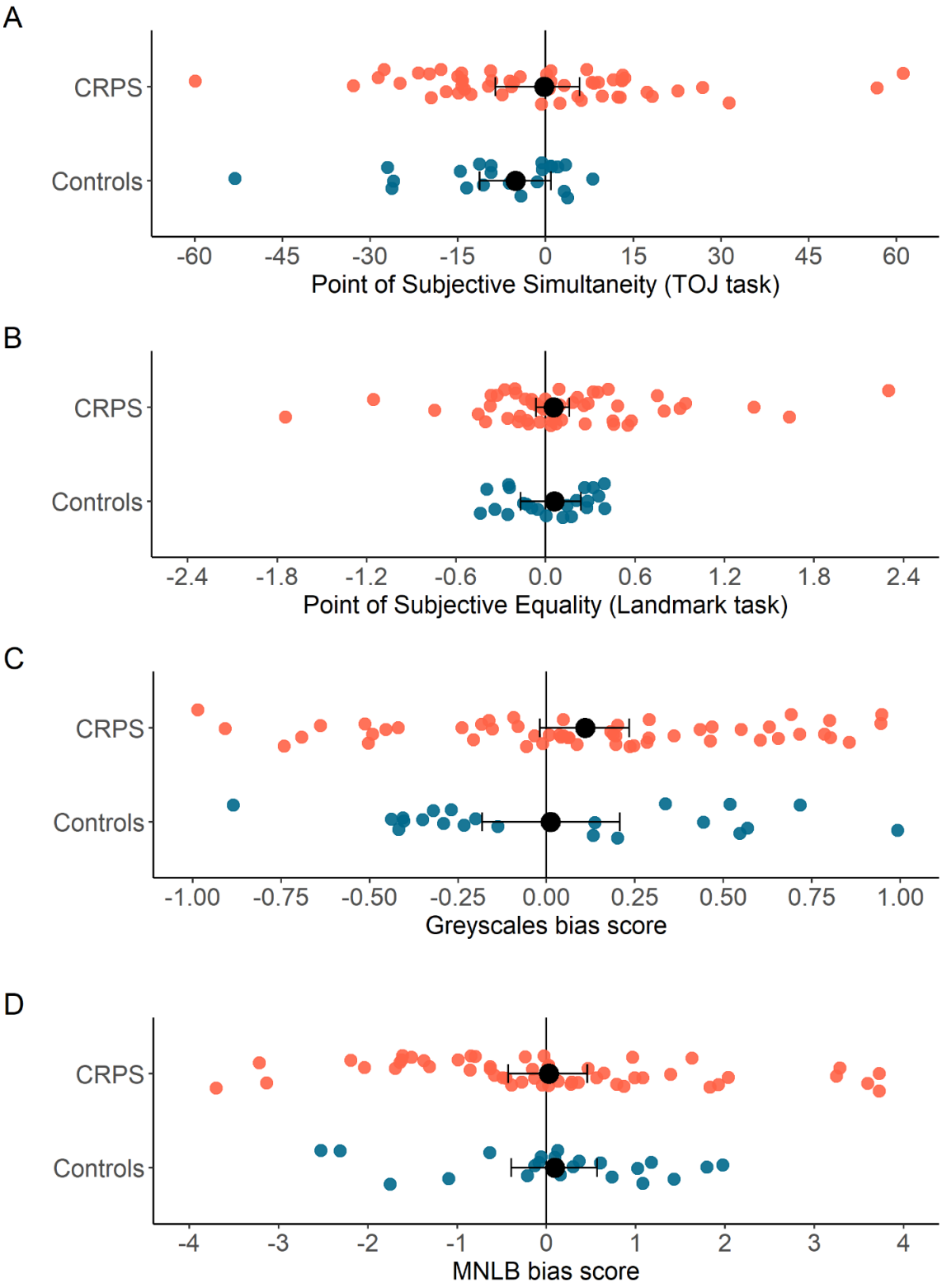

Figure 2. Results of the experimental tests of visuospatial attention (A-C) and the mental representation of space (D). Smaller circles represent individual data from participants with CRPS (orange) and pain-free control participants (blue). Larger black circles represent the group median (A, B) and mean (C, D) scores with bootstrapped 95% confidence intervals (error bars). (A) The Point of Subjective Simultaneity on the Temporal Order Judgement task indicates by how many milliseconds the light on the affected side should precede (negative values) or follow (positive values) the light on the unaffected side for the two lights to be perceived as simultaneous. (B) The Point of Subjective Equality on the Landmark task indicates by how many degrees of visual angle

the pair of landmarks should be offset from being truly equidistant to central fixation towards the affected side (negative values) or towards the unaffected side (positive values) for the two landmarks to be perceived as equidistant. (C) The bias score on the Greyscales task indicates to what extent the participants were basing their darkness judgements on the side of the stimuli corresponding to their unaffected side (negative values) or to their affected side (positive values). (D) The bias score on the Mental Number Line Bisection task indicates to what extent participants' subjective midpoint of the mental number line was shifted towards the numbers corresponding to their unaffected side (e.g. higher numbers for participants with left-CRPS; negative values) or to their affected side (e.g. smaller numbers for participants with left-CRPS; positive values). Negative scores for each of the measures depicted in this figure would indicate reduced attention to or (mental) representation of the affected side of space.

3.4.4. Spatially-defined motor function

3.4.4.1. Linear mixed models regressions on movement initiation and execution times

After excluding incorrect and missed trials, we computed mean movement initiation time and movement execution time for each combination of VF and hand Starting Position. The tasks performed with the affected (CRPS n = 43 [initiation], 45 [execution]; control n = 21) and unaffected limb (CRPS n = 50; control n = 18) were analysed separately.

The data for this task were analysed using four bootstrapped linear mixed models regression analyses. The four outcome measures were initiation times and execution times for both the affected and unaffected limb. The fixed effects for each analysis were Group (participants with CRPS, healthy controls), Starting Position (affected, central, unaffected), VF (affected, unaffected) and their interactions. Participant ID was entered as a random effect in each analysis. As this method is robust to the presence of outliers and missing values (Wu, 2009), we used unprocessed data (i.e. data prior to replacement of group-level outliers and missing values). A variable made a significant contribution to predicting the outcome variable when the 95% CI around the regression coefficient (B) did not include zero. As our main objective was to assess the differences in motor function between participants with CRPS and healthy controls, here we only summarise those significant main effects and interactions that involved Group. The full results for all four regression analyses are reported in Supplementary Material.

The terms of the regression analyses that were of most interest in the present study were the interactions between Group and VF; and between Group, Starting Position, and VF. The results showed that these terms did not significantly contribute to the prediction of movement initiation and execution times for either the affected or unaffected hand (i.e. all confidence intervals around the relevant regression coefficients included 0; see Supplementary Table S1).

We found significant main effects of Group on initiation times for both limbs (affected B = 0.19, BCa 95% CI [0.16, 0.22]; unaffected B = 0.07, BCa 95% CI [0.05, 0.10]), indicating that, regardless of the hand Starting Position or the VF in which the target appeared, participants with CRPS were slower to initiate movements with their affected (Mdn = 553.28, BCa 95% CI [488.40,

582.85]) and unaffected (*Mdn* = 459.50, BCa 95% CI [438.19, 485.04]) limbs compared to the initiation times of the control participants with their matched "affected" (*Mdn* = 416.09, BCa 95% CI [403.52, 435.54]) and "unaffected" (*Mdn* = 412.74, BCa 95% CI [394.47, 438.38]) limbs. The analyses of movement execution times also showed significant main effects of Group for both limbs (affected *B* = 0.44, BCa 95% CI [0.36, 0.52]; unaffected *B* = 0.11, BCa 95% CI [0.08, 0.15]). Specifically, execution of movement with the affected (*Mdn* = 970.45, BCa 95% CI [907.66, 1012.56]) and unaffected (*Mdn* = 820.14, BCa 95% CI [733.29, 858.03]) limbs among participants with CRPS was slower compared to execution times with the matched "affected" (*Mdn* = 677.37, BCa 95% CI [620.88, 746.19]) and "unaffected" (*Mdn* = 678.87, BCa 95% CI [586.43, 756.35]) limbs in the control group. These effects are consistent with overall slowing of initiation and execution of movements with both affected and unaffected limbs in participants with CRPS relative to healthy controls.

The regression model for movement execution times with the unaffected limb showed that the term for the interaction between Group and affected versus unaffected Starting Position was significant (*B* = 0.06, BCa 95% CI [0.002, 0.12]). For participants with CRPS, the difference in execution times for movements originating from the unaffected (*Mdn* = 858.14, BCa 95% CI [795.38, 887.98]) compared to affected (*Mdn* = 801.83, BCa 95% CI [722.31, 811.46]) Starting Positions was larger relative to the same difference for controls (unaffected *Mdn* = 692.69, BCa 95% CI [643.87, 769.59]; affected *Mdn* = 658.19, BCa 95% CI [590.84, 771.66]), regardless of the VF in which the targets appeared (Figure 3). This pattern is consistent with directional bradykinesia for the affected space: slowing of movements directed toward the affected side of space relative to movements directed toward the unaffected side of space. In the same regression model, the term for the Group by affected versus central Starting Position interaction was not significant (*B* = 0.01, BCa 95% CI [-0.04, 0.06]).

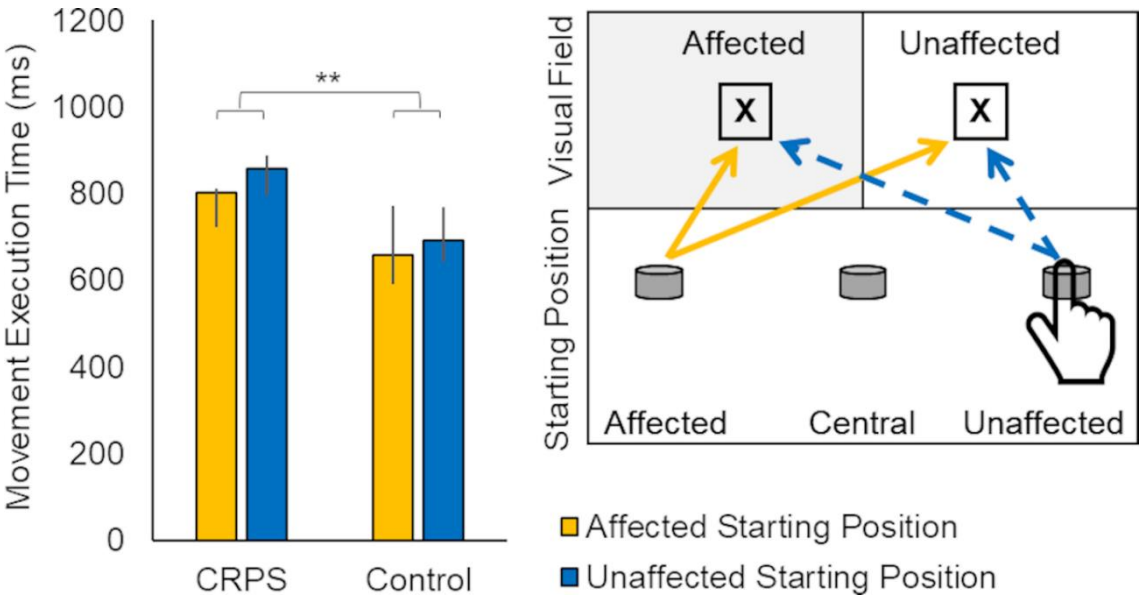

Figure 3. Interaction between Group and Starting Position on execution times of movements performed with the unaffected limb starting from the affected compared to unaffected positions. Bars represent CRPS and control participants' median execution times (error bars: BCa 95% CIs) with the unaffected hand from affected (yellow) and unaffected (blue) Starting Positions, averaged across two Visual Fields. **The interaction is significant at the level of $p_{adjusted} < .01$. The inset panel (right) illustrates slower execution of movements to the targets (X) in either Visual Field from the unaffected Starting Position (blue dashed arrows), relative to the affected Starting Position (yellow solid arrows).

3.4.4.2. Analyses of directional hypokinesia and bradykinesia indices

To dissociate any signs of directional hypokinesia and bradykinesia from potential visual "neglect-like" deficits, biomechanical constraints, and lengths of movement pathways from different starting positions, we additionally analysed specific indices for each limb separately. We calculated two indices of directional hypokinesia towards the affected side based on those used in previous research on spatial motor biases in stroke patients (Sapir et al., 2007). The relevant movement pathways and formulae are represented in Figure 4. The first index (A; Figure 4a) describes the difference in initiation times towards the affected VF with respect to the unaffected VF, depending on the direction of movements (that is, as a function of starting position). We derived a second index (B; Figure 4b), which in contrast to Index A, does not involve comparing a movement within one side of space to one across the body midline (and therefore over a longer pathway). Index B directly describes the relative slowing (if any) of initiations of movements to the affected VF when making movements of the same physical length directed toward the affected side compared to movements directed toward the unaffected side (Figure 4b). Larger (more positive) values of Indices A and B indicate greater directional hypokinesia towards the affected side. To account for the possibility of directional hypokinesia towards the *unaffected* side (i.e. in the direction opposite to hypothesized "neglect-like" motor deficits), we computed two additional indices (C and D; Figure 4c,d), which were not considered in Sapir et al.'s (2007) study. Indices C and D are analogous to Indices A and B, respectively, and describe relative slowing of

movement initiation toward the unaffected side with respect to the affected side. Larger values of Indices C and D indicate greater directional hypokinesia towards the unaffected side. We calculated the same four indices for movement execution times to examine any signs of directional bradykinesia. We examined differences between participants with CRPS and healthy controls on each index and for each hand through separate between-group contrasts.

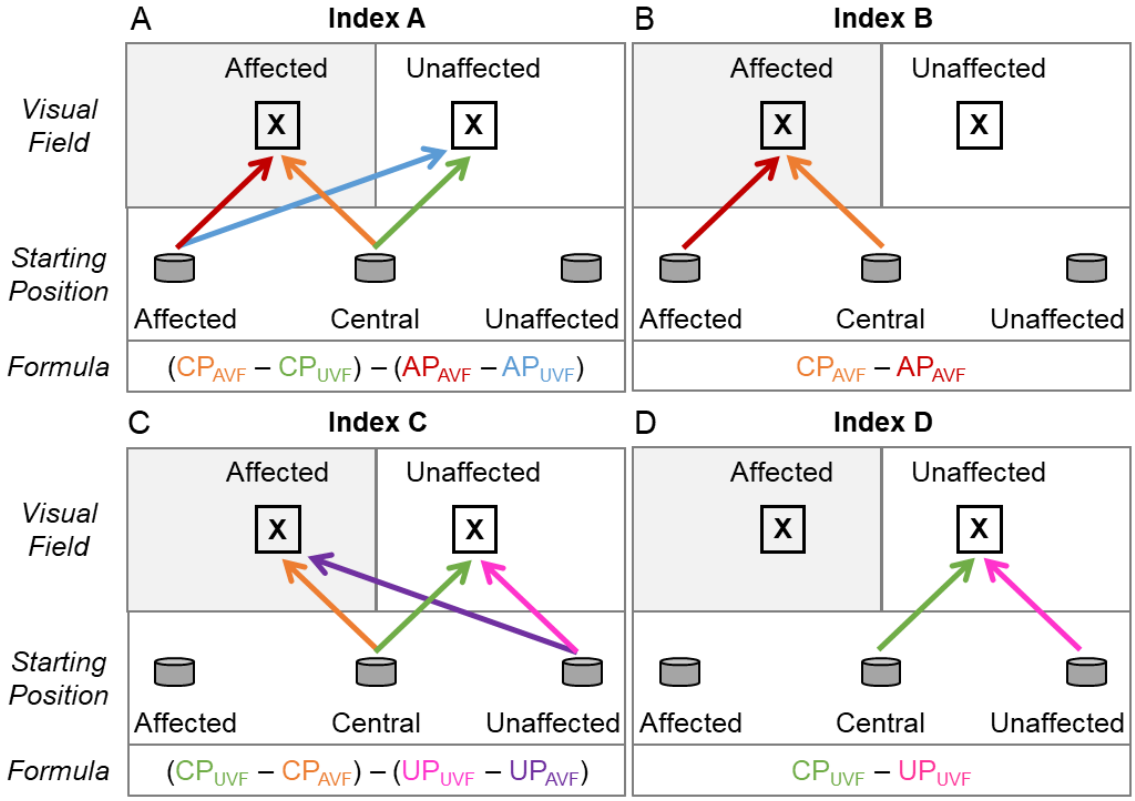

Figure 4. Movement pathways and formulae used to calculate indices of directional hypokinesia and bradykinesia towards the affected (A, B) and unaffected (C, D) side of space. The arrows indicate the direction of movement from hand Starting Position (affected, AP; central, CP; and unaffected, UP) to the targets (X) appearing in the affected (AVF) or unaffected (UVF) Visual Field. Indices for each hand were computed using movement initiation (hypokinesia) or execution (bradykinesia) times according to the formulae represented in the bottom segments of each panel. More positive values for Indices A (A) and B (B) would indicate greater directional hypokinesia/bradykinesia towards the affected side; more positive values for Indices C (C) and D (D) would indicate greater directional hypokinesia/bradykinesia towards the unaffected side.

After Holm-Bonferroni correction, Mann-Whitney *U* tests did not show significant differences between the CRPS participants' and controls' indices of directional hypokinesia and bradykinesia towards the affected side ($Us \geq 323.00$, $ps_{adjusted} \geq .062$, $ds \leq 0.47$), with one exception. Index A (Figure 4a) for movement execution with the unaffected limb was significantly more positive among the CRPS participants (*Mdn* = 100.16, BCa 95% CI [84.22, 125.09]) compared to control participants (*Mdn* = 59.42, BCa 95% CI [39.37, 73.29]), $U = 294.00$, $p_{adjusted} = .032$, $d = 0.55$. Analysis of the indices of directional hypokinesia and bradykinesia towards the unaffected side showed that the CRPS participants' Index C (Figure 4c) for movement initiation with the affected limb (*Mdn* = 18.05, BCa 95% CI [3.02, 30.89]) was significantly more positive than the controls'

Index C (*Mdn* = 0.19, BCa 95% CI [-13.01, 8.25]), $U = 272.00$, $p_{adjusted} = .016$, $d = 0.63$. There were no other significant between-group differences ($Us \geq 318.00$, $ps_{adjusted} \geq .072$, $ds \leq 0.46$). Overall, these results indicate that there was some evidence for participants with CRPS showing significant directional bradykinesia towards the affected side (Index A) when using the unaffected limb, but also for significant directional hypokinesia towards the unaffected side (Index C) when using the affected hand, compared to controls.

Considering that only a subset of stroke patients in Sapir et al.'s (2007) study presented with significant directional hypokinesia (9 out of 52 patients, i.e. 17%, in a task performed only with the unaffected hand; identified based on z-scores compared to controls' distribution), we explored whether there was a subgroup of CRPS patients showing this deficit. For this purpose, we compared each individual patient's Indices A and B for movement initiation and execution with the affected and unaffected hand to the controls' mean indices using Crawford *t*-tests (Crawford & Howell, 1998). A patient was classified as showing signs of directional hypokinesia or bradykinesia towards the affected side if both their Indices (A and B) were significantly more positive than controls' mean indices ($ps < .05$). For balance, we used the same method to explore what proportion of patients presented with significant directional hypokinesia or bradykinesia towards the *unaffected* side, that is, had more positive Indices C and D. Table 2 summarises the results. Overall, when the affected limb was used, directional hypokinesia and bradykinesia towards the unaffected side was more prevalent than towards the affected side, and the opposite tendency was seen when the unaffected limb was used. However, the absolute number of patients with signs of directional hypokinesia and bradykinesia when the unaffected limb was used was low.

Table 2 *Proportion of participants with CRPS who showed signs of directional hypokinesia or bradykinesia towards the affected side (Indices A and B) or towards the unaffected side (Indices C and D)*

	Directional hypokinesia	Directional bradykinesia	Directional hypokinesia	Directional bradykinesia
	for the affected side[a]		for the unaffected side[b]	
Affected hand	3 / 43 (6.98%)	4 / 45 (8.89%)	8 / 42 (19.05%)	7 / 43 (16.28%)
Unaffected hand	4 / 50 (8.88%)	1 / 50 (2.00%)	0 / 50 (0.00%)	0 / 49 (0.00%)

[a]Number of individual participants with CRPS (out of the total number of participants with CRPS with complete data on the specific indices) whose Indices A and B were both significantly more positive compared to mean indices of control participants; [b]Number of individual participants with CRPS whose Indices C and D were both significantly more positive compared to mean indices of control participants.

3.4.5. Relationships between neuropsychological changes and clinical symptoms of CRPS

To investigate the relationships between neuropsychological changes and clinical symptoms of CRPS, we conducted best subsets regression analyses on the data from participants with CRPS. Due to the exploratory nature of this analysis, we took this automated approach to avoid any

biased selection of the predictors. The pool of potential predictors of each outcome included all measures of neuropsychological, sensory, motor, autonomic, and psychological changes, as measured by computer-based tasks, clinical and sensory assessments, and self-reported questionnaires. Best subsets regressions were determined for the outcome variables BPI pain severity and CRPS severity score, as key measures of clinical severity of this condition. We also performed regressions on those neuropsychological outcomes on which participants with CRPS differed from controls: BPDS, movement initiation time with the affected hand, movement initiation time with the unaffected hand, movement execution time with the affected hand, and movement execution time with the unaffected hand. The only pre-selection involved removing the variables that were not linearly related to the outcome of interest, to satisfy the assumption of linearity. To address co-linearity, when two variables were highly correlated with each other (Pearson's $r > .70$; see Figure S2), only the one with higher correlation with the outcome was entered into regression analysis. This was the case for the following pairs of variables: current pain intensity and BPI pain severity; BPI pain severity and BPI pain interference; movement initiation time of the affected and unaffected hand; and signed and absolute temperature difference. Considering our sample size (N = 54), we compared best subsets regression models that included up to five predictors of each outcome. The best model was chosen based on the combination of the highest adjusted R^2, lowest Bayesian Information Criterion (BIC), lowest Akaike Information Criterion (AIC), and lowest Mallows' Cp. Because each of these criteria may favour different models, and to address the issue of potential overfitting, we also considered the criterion of the lowest prediction error (CV) based on five-fold cross-validation (Lever et al., 2016). That is, we divided the data set into five subsets, whereby each subset (20%) served as test data and the remaining subsets (80%) as training data. The coefficients and related statistics for the chosen predictors of the best fits regression models for all outcome variables are summarised in Table 3. In the text we also reported adjusted R^2, AIC, and CV as the most consistent indicators of the best model fits.

Table 3 *Model summaries for best subsets regression analyses*

Outcome	Predictors	*B*	*SE B*	*ß*	*t*	*p*
BPI - Pain severity	(Intercept)	1.45	1.18		1.23	0.227
	BPDS*	0.08	0.02	0.52	3.83	< 0.001
	Grip strength*	-2.79	0.95	-0.47	-2.94	0.006
	Pain Detect Questionnaire*	0.11	0.04	0.37	2.86	0.007
	Finger-to-palm distance*	2.32	1.01	0.35	2.30	0.027
	Movement initiation time (affected hand)	-0.002	0.001	-0.23	-1.59	0.121
CRPS severity score	(Intercept)	11.90	0.61		19.64	< 0.001
	Grip strength*	-2.38	0.61	-0.45	-3.89	< 0.001
	BPI - Pain interference*	0.22	0.08	0.33	2.81	0.007
BPDS	(Intercept)	-8.67	4.37		-1.98	0.055
	Movement initiation time (affected hand)*	0.02	0.01	0.37	3.80	0.001
	Current pain intensity*	2.12	0.60	0.37	3.53	0.001
	Profile of Mood States*	0.12	0.04	0.36	3.34	0.002
	Two-Point Discrimination*	-6.81	2.32	-0.28	-2.93	0.006
	Oedema	1.75	1.11	0.15	1.57	0.124
Movement initiation time (affected hand)	(Intercept)	494.99	92.35		5.36	< 0.001
	BPDS*	8.32	2.47	0.46	3.36	0.002
	CRPS duration*	2.27	0.63	0.38	3.59	0.001
	Current pain intensity*	-35.64	13.96	-0.34	-2.55	0.015
	Grip strength*	-220.71	77.74	-0.32	-2.84	0.007
	Allodynia*	2.62	1.10	0.31	2.39	0.022
Movement initiation time (unaffected hand)	(Intercept)	239.35	76.47		3.13	0.003
	BPDS*	5.25	1.63	0.44	3.23	0.002
	CRPS duration*	1.38	0.40	0.42	3.48	0.001
	Current pain intensity*	-20.54	9.05	-0.30	-2.27	0.028
	Δ EHI	0.49	0.25	0.24	1.99	0.053
	Pain Detect Questionnaire	5.00	3.21	0.21	1.56	0.126
Movement execution time (affected hand)	(Intercept)	2133.83	819.75		2.60	0.013
	Grip strength*	-775.09	295.88	-0.43	-2.62	0.013
	Δ EHI *	2.97	1.30	0.36	2.28	0.028
	CRPS severity score	-94.19	56.09	-0.28	-1.68	0.101
	Greyscales bias score	-252.45	159.76	-0.20	1.58	0.122
	Age	6.73	5.37	0.16	1.25	0.217
Movement execution time (unaffected hand)	(Intercept)	980.25	295.65		3.32	0.002
	Finger-to-palm distance*	-296.99	97.50	-0.44	-3.05	0.004
	Age*	4.57	2.05	0.29	2.23	0.031
	CRPS severity score	-29.23	19.22	-0.24	-1.52	0.135
	Pain Detect Questionnaire	8.22	4.94	0.23	1.67	0.103
	MNLB score	-19.05	16.06	-0.15	1.19	0.242

Note. *Statistically significant predictors. BPI = Brief Pain Inventory; BPDS = Bath CRPS Body Perception Disturbance Scale; Δ EHI = absolute pre- to post-CRPS change in Edinburgh Handedness Inventory score; MNLB = Mental Number Line Bisection.

3.4.5.1. Predictors of pain and CRPS symptoms severity

The best fits regression models for the predictions of BPI pain severity and CRPS severity score are summarised in Table 3. Higher pain severity (as measured by BPI) was best predicted by more severe body perception disturbance, weaker grip strength in the affected hand, a greater neuropathic component of pain, greater range of movement in the affected hand, and faster movement initiation with the affected hand (non-significant predictor), $F(5, 37) = 9.12$, $p < .001$, *adj*. $R^2 = .49$, AIC = 29.33, CV = 1.31. Larger CRPS severity scores were best predicted by weaker grip strength in the affected hand and higher pain interference, $F(2, 51) = 20.59$, $p < .001$, *adj*. $R^2 = .43$, AIC = 26.30, CV = 1.22.

3.4.5.2. Predictors of cognitive changes in CRPS

The best fits regression models for the predictions of BPDS and overall movement initiation and execution times with the affected and unaffected hands are summarised in Table 3. More severe body perception disturbance (higher BPDS score) was best predicted by slower movement initiation time with the affected hand, higher current pain intensity, higher mood disturbance score, more precise two-point discrimination on the affected limb, and greater swelling of the affected limb (non-significant predictor), $F(5, 37) = 15.73$, $p < .001$, *adj*. $R^2 = .64$, AIC = 175.30, CV = 7.51. Slower initiation of movements with the affected hand was best predicted by more severe body perception disturbance, longer CRPS duration, lower current pain intensity, weaker grip strength in the affected hand, and more severe allodynia on the affected limb, $F(5, 37) = 10.58$, $p < .001$, *adj*. $R^2 = .53$, AIC = 434.52, CV = 152.47. Movement initiation times with the unaffected hand shared some of the same predictors. Specifically, slower movement initiation was best predicted by more severe body perception disturbance, longer CRPS duration, lower current pain intensity, greater change in handedness after CRPS onset, and a greater neuropathic component of pain, although the latter two factors were not significant predictors, $F(5, 44) = 6.59$, $p < .001$, *adj*. $R^2 = .36$, AIC = 475.81, CV = 129.60. Slower movement execution when using the affected hand was best predicted by weaker grip strength in the affected hand, greater change in handedness after CRPS onset, lower CRPS severity score, greater attention to the affected side of space on greyscales task, and older age, $F(5, 39) = 4.81$, $p = .002$, *adj*. $R^2 = .30$, AIC = 559.36, CV = 492.89. However, only the first two factors were statistically significant predictors of movement execution time. For the unaffected hand, slower movement execution was best predicted by smaller range of movement in the affected hand, older age, lower CRPS severity score, greater neuropathic component of pain, and greater bias toward the affected side of the mental representation of space, $F(5, 44) = 4.23$, $p = .003$, *adj*. $R^2 = .25$, AIC = 524.46, CV = 182.27. Only the first two factors significantly predicted movement execution time with the unaffected limb.

4. Discussion

We conducted a detailed examination of changes in spatial cognition in CRPS using sensitive experimental methods in a larger than previous research has used sample. Contrary to our hypotheses, our findings across measures of visuospatial attention and mental representation of space consistently showed no evidence of any spatial biases among people with CRPS compared to pain-free control participants, and there was very little evidence for directional motor deficits. We also found no support for any clinical relevance of changes in spatial cognition for the severity of pain and other symptoms of CRPS.

4.1. Visuospatial attention

Although previous studies have used TOJs to provide evidence for reduced tactile (Moseley et al., 2009, 2012; Reid et al., 2016) and visual (Bultitude et al., 2017; Filbrich et al., 2017) attention to the affected relative to unaffected side in people with CRPS, we found no such visuospatial attention bias on our TOJ task. One notable difference between these previous studies and ours is that most of them (Bultitude et al., 2017; Moseley et al., 2009; Reid et al., 2016) asked participants only to indicate which stimulus occurred *first*. This might mean that previous results were influenced by response bias, that is, a preference of one response over the other when the participant is uncertain about temporal order of the stimuli (Filbrich et al., 2016; Spence & Parise, 2010). Distorted perception of the CRPS-affected limb can involve hostile feelings, such as repulsion and hate (Lewis et al., 2007), which resemble misoplegia after brain injury (Bartolomeo et al., 2017). Thus, particularly when a verbal response is required (Bultitude et al., 2017), participants with CRPS might be reluctant to say "left" or "right", depending on the side corresponding to their affected limb. Here we controlled for potential response bias by including a separate block of the TOJ in which participants were asked to indicate which stimulus occurred *second* (in addition to "which occurred first" block). The two previous studies that also controlled for response bias in a similar way, reported mixed findings regarding spatial biases on tactile TOJs (reduced attention to the affected side, Moseley et al., 2012, and normal performance, Filbrich et al., 2017). Thus, the response bias might be an important factor in the performance of CRPS patients on the TOJ task. Consistent with our findings, Filbrich et al. (2017) found no apparent shift of visual attention when the participants' hands were kept close to the trunk (outside of the visual field). However, when the stimuli appeared in immediate proximity of participants' hands, they found a significant visuospatial bias even when controlling for response bias. This is in keeping with a proposal that spatial biases might only be present (or exacerbated) when body-relevant information is highly salient to the task (Reid et al., 2016). Thus, our results do not rule out the possibility that people with CRPS might still present with spatial biases in the tactile modality and / or related to other bodily information.

We also found that people with CRPS did not present with any biases on two additional tests of visual attention to and representation of near space. The Greyscales and Landmark tasks have not been previously tested in CRPS, but have sufficient sensitivity to detect visuospatial biases in brain-injured neglect patients (Mattingley et al., 2004), neurologically healthy individuals (Nicholls et al., 1999), and upper-limb amputees (Makin et al., 2010). Overall, consistently unbiased performance on the experimental tests of covert and overt attention to and representation of near visual space in this study suggests normal visuospatial cognition in CRPS. These findings agree with another study that also did not demonstrate any visuospatial biases in the speed of orienting saccades towards targets in either side of space (Filippopulos et al., 2015).

4.2. Mental representation of space

Representational neglect has not been extensively studied in CRPS, and not in combination with sensitive tests of visuospatial attention. One group study reported a shift of subjective midpoint of mental number line in the direction corresponding to the unaffected side (Sumitani et al., 2014), consistent with representational neglect after brain injury (Zorzi et al., 2002). However, a shift in the opposite direction was also reported in a single CRPS patient (Christophe, Delporte, et al., 2016; Jacquin-Courtois et al., 2017). While using the same MNLB task as Sumitani et al. (2014), we additionally presented number pairs not only in ascending, but also in descending order. Averaging the responses from these two conditions accounts for a potential tendency to report subjective midpoints as numbers closer to the starting point on mental number line, that is nearer the first number from a pair. Having controlled for these potential response biases, we did not find any systematic deviations from objective midline in participants with CRPS, nor any differences between the performance of participants with CRPS and controls.

4.3. Spatially-defined motor function

In general, there are four potential explanations of impaired motor function in CRPS. First, diagnostic criteria for CRPS include motor signs, such as weakness, decreased range of movement, or dystonia (Harden et al., 2010); thus physical pathology of the affected limb itself can result in impaired motor performance. Second, learned underutilization of the affected limb can develop through initial immobilization following a trauma, pain avoidance, and compensatory use of the unaffected limb (Punt et al., 2013). These learned behaviours can reinforce reduced use of the CRPS-affected limb and further deter its motor function. Third, motor "neglect-like" impairment can account for reduced or slower movements of the affected limb that cannot be attributed to any peripheral pathology, as well as movements performed in / towards the affected side of space, regardless of which limb is used (Laplane & Degos, 1983; Mattingley et al., 1992). Thus, motor function can be impaired in a spatially-defined manner consistent with neglect of the CRPS-affected limb and side of space. Fourth, central deficit of motor control can account for generalised / bilateral motor impairment that cannot be explained by peripheral pathology or

deficits in spatial cognition. While the motor signs of CRPS and learned underutilization can only account for motor deficits specific to the CRPS-affected limb, the motor neglect and reorganization of central motor circuits additionally address spatially-defined and bilateral motor deficits found in CRPS, respectively. In the present study, we tried to dissect the motor neglect hypothesis from the alternative explanations of impaired motor function in CRPS.

Consistent with motor neglect of the affected side, people with CRPS previously reported having to focus their attention on the painful limb to move it (Galer et al., 1995; Galer & Jensen, 1999). Furthermore, their motor performance on speeded button pressing and circle drawing tasks was slower, more variable, and less accurate when they used the affected limb, and also when movements were performed in the affected side of space regardless of which hand they used (Reid et al., 2018). These findings suggest spatially-defined disruption of motor control that cannot be explained by physical pathology or learned underutilization of the affected limb (although the bilateral spatially-defined motor deficits did not replicate in another group study, Christophe, Chabanat, et al., 2016, and a case study, Christophe, Delporte, et al., 2016, which both used similar motor tasks). We tested for the first time if people with CRPS show *directional* motor neglect, that is, slowing of initiation (directional hypokinesia) or execution (directional bradykinesia) of movements directed towards the affected relative to unaffected side of space, regardless of which limb is used (Heilman, Bowers, & Watson, 1983; Mattingley, Bradshaw, & Phillips, 1992; Sapir et al., 2007).

People with CRPS in our study showed some evidence of slower execution of movements of the unaffected hand when they were directed towards the affected compared to unaffected side of space, consistent with hypothesised directional bradykinesia towards the affected side. This slowing cannot be attributed to perceptual neglect, as it occurred regardless of reaching to targets in the affected or unaffected side of space. Nor can it be attributed to physical pathology or learned underutilization of the CRPS-affected limb, as participants used the unaffected hand. On an individual level, some cases could be classified as showing consistent directional deficits towards the affected side with either hand, although the number was very few (< 10%). This is consistent with the finding that a relatively small proportion of brain-injured patients presented with directional hypokinesia towards the contralesional side when using their ipsilesional hand on the same task (17%, Sapir et al., 2007). However, in the present study a larger proportion of individuals with CRPS (16-19%) was classified as showing directional slowing towards the *un*affected side, but only when using the affected hand. Furthermore, on a group level, people with CRPS showed no other signs of directional hypokinesia or bradykinesia towards the affected or unaffected side for either hand that would differentiate them from pain-free controls. Most of the effects observed in both groups could be explained by general (non-directional) biomechanical constraints such as differences in movement pathways and crossing the body midline (see Supplementary Material). Therefore, when the differences between participants with CRPS and

pain-free controls are considered as a whole, the results do not support the presence of directional motor deficits.

Although we did not find systematic evidence for directional motor deficits resembling motor neglect, our results demonstrate that people with CRPS had overall slowing of initiation and execution of the movements of both limbs as compared to pain-free controls. Previous sensitive kinematic analyses also showed impairment on motor tasks performed with both hands (Schilder et al., 2012) or with the unaffected hand (Ribbers et al., 2002) in CRPS compared to pain-free individuals. This cannot be explained by peripheral pathology or learned underutilization of the CRPS-affected limb. Instead, bilateral slowing could either reflect a central motor deficit, or general decrease in psychomotor speed that is often found in patients with chronic pain. Neuroimaging evidence suggests that such movement deficits could be related to altered central motor circuits, that is decreased inhibition of bilateral motor cortex (Juottonen et al., 2002; Schwenkreis et al., 2003), and its increased bilateral activation during movements of the affected hand relative to rest (Maihofner et al., 2007) in CRPS. Therefore, slowing of initiation and execution of movements with both limbs could be related to functional reorganization in cortical motor networks. A likely alternative explanation is generalised impairment of psychomotor speed, which has been consistently reported in chronic pain conditions such as diabetic neuropathy, fibromyalgia, low back pain, or osteoarthritis (Higgins et al., 2018). Consistent with previous studies that associated slower psychomotor performance with higher pain intensity (Lee et al., 2010; Pulles & Oosterman, 2011), our results demonstrate its predictive value for slower movement initiation with both hands. We cannot rule out that fatigue or analgesic medication could also contribute to an overall decrease in psychomotor speed in individuals with chronic pain, although existing evidence does not support the latter alternative (Kendall et al., 2010; Landrø et al., 2013). The overall slowing of movement found in our sample might not be specific to CRPS but rather characterise people with chronic pain more generally, comparably to psychomotor slowing in patients after a stroke irrespective of hemispatial neglect (Harvey & Rossit, 2012; Konczak & Karnath, 1998; Rossit et al., 2009), or in other chronic diseases (Alosco et al., 2012; Perry et al., 2008). The current behavioural data does not allow us to dissociate the two alternative explanations of bilateral slowing of movement (altered cortical motor networks and overall psychomotor slowing), however, future studies could address this issue by implementing neuroimaging methods, pain-control groups, and controlling for fatigue.

4.4. Relationships between clinical signs, motor deficits, and neuropsychological changes in participants with CRPS

An additional aim of our study was to identify any relationships between clinical signs, motor deficits, and cognitive / psychological changes of our participants with CRPS. Recognizing that our analyses were exploratory, we offer only tentative explanations of the observed effects that should be tested in further research. Across different clinical and experimental measures,

performance of CRPS participants on our battery of spatial cognition tests did not contribute to the prediction of the clinical outcomes. Therefore, these neuropsychological changes might not pertain to the clinical signs of CRPS, which calls into question the role of cortical reorganisation in the manifestation of the disorder and potential benefits of neurocognitive treatments that target deficits in spatial cognition (e.g. prism adaptation, Torta, Legrain, Rossetti, & Mouraux, 2016). In fact, overall, the key clinical measures of pain and CRPS severity were predicted by other clinical measures. Specifically, both pain and CRPS symptom severity were predicted by weaker grip strength, and pain was additionally predicted by reduced range of movement in the affected hand, highlighting the relevance of motor impairment. More severe sensory abnormalities consistent with features of neuropathic pain also predicted greater pain severity. Furthermore, we found a relationship between the severity of CRPS symptoms and the extent to which pain interfered with daily life, including work, social life, mobility, sleep, or mood (however, as pain interference was co-linear with pain severity, CRPS severity could be related to either).

From all the measures that could imply cortical reorganisation relevant to higher cognition, only self-reported body perception disturbance (BPDS scores) was related to pain severity and motor function. The BPDS measures subjective ownership of the affected limb; awareness of its position; attention to and valence of feelings towards the painful extremity; as well as perceived distortions of its size, shape, and / or weight (Lewis & McCabe, 2010). Higher pain intensity was previously linked to reporting greater distortions of body representation, both on the BPDS (Lewis & Schweinhardt, 2012) and neglect-like symptoms questionnaire (which measures partly overlapping construct of body ownership; Frettlöh et al., 2006; Wittayer et al., 2018). Distorted cognitive representation of the affected limb could reflect reorganization in the somatosensory cortical areas corresponding to that limb. People with weaker activation in the somatosensory cortex contralateral to the CRPS-affected hand (Pleger et al., 2006) and those with greater body perception disturbance (Lewis & Schweinhardt, 2012) had worse tactile discrimination abilities on the affected hand and higher levels of pain. However, there is no evidence of direct link between subjective representation of the affected limb and its somatosensory cortical representation. While previous evidence suggested that the cortical map of the affected hand in people with CRPS is smaller relative to the unaffected hand and healthy controls (Di Pietro et al., 2013), a more recent, high quality study found that these maps are largely comparable and CRPS is not associated with reorganisation of the somatosensory cortex (Mancini et al., 2019). Our analyses showed that, in addition to pain and tactile discrimination thresholds, greater body perception disturbance was also predicted by greater mood disturbance. This is in line with previously demonstrated relationships between psychological distress and scores on the neglect-like symptoms questionnaire (Michal et al., 2016; Wittayer et al., 2018). Therefore, subjective body representation might be related to sensory and psychological factors, but not necessarily taken as evidence of cortical reorganisation in CRPS.

Overall slowing of movements was the only outcome from our battery of spatial cognition and motor function tests that differentiated people with CRPS from healthy controls. We found that those with slower movement initiation with the affected and unaffected hands had more severely distorted body perception. This suggests that subjective cognitive representations can contribute to motor function in CRPS. Body representation relies on combined proprioceptive, vestibular, somatosensory, and visual information that interact with the motor control system to guide actions (Head & Holmes, 1912). Higher scores on the neglect-like symptoms questionnaire (which, like the BPDS, also regards disownership of the affected limb; Frettlöh et al., 2006) were previously linked to greater motor impairment and disability in individuals with CRPS (Kolb et al., 2012). While these distortions in body perception primarily concern the affected limb, arm position sense (which relies on proprioception) has been found to be impaired bilaterally in CRPS (Brun et al., 2019; Lewis et al., 2010). Thus, deficits in proprioception in both limbs might slow down movement initiation due to uncertainty about their current positions. Slowing of movement initiation with both limbs was also predicted by longer CRPS duration, consistent with the ideas that central mechanisms would have greater contribution to CRPS symptomatology in more chronic stages of the disease (Birklein & Schlereth, 2015; Bruehl & Chung, 2015; Veldman et al., 1993) or that psychomotor speed would decrease with longer duration of chronic pain (Jongsma et al., 2011; Ryan, 2005). We also found that people with more weakness in the affected hand and greater change in hand preference following CRPS onset (taken as an approximation of functional impact of CRPS) were slower to initiate and execute movements with the affected extremity. This is consistent with the "learned non-use" hypothesis (Punt et al., 2013): that ongoing underutilization of the CRPS-affected limb leads to atrophy, muscle weakness, and movement slowing, further exacerbating or maintaining motor deficits. Taken together, our results suggest that not only functional underutilization of the affected limb, but also bilateral central mechanisms of motor control or pain-related psychomotor slowing and subjective body perception, might contribute to the extent of motor impairment in CRPS.

Overall, our exploratory analyses do not support the conclusion that changes in spatial cognition are relevant for the manifestation and severity of CRPS symptoms. Instead, body representation and motor abilities appear to be important determinants of CRPS pain and symptom severity.

4.5. Strengths and limitations

Our results suggest that previously reported "neglect-like" changes in spatial cognition in CRPS might have been overstated. There are several advantages of the present study that strengthen our confidence in this conclusion. We systematically tested for any visuospatial and spatially-defined motor biases using a battery of sensitive tests in a group of people with CRPS that was two-to-five times larger than tested before on the TOJs or spatial motor tasks. One possible reason for the disparity between our results and those of previous studies is that there are individual differences in the extent to which cognitive function is affected in CRPS. Considering the high

variability in the clinical presentation of CRPS, different trajectories of symptom development and strategies to deal with pain might lead to distinct patterns of cognitive changes (Marinus et al., 2011). In other words, in heterogeneous conditions such as CRPS, effects might arise in small sample studies that may not replicate, potentially due to the chance selection of more individuals who happen to present with a certain deficit. Consistent with this account of variability in past results, our participants with CRPS showed a larger range of individual bias scores on the spatial tasks than the controls (Figure 2). However, since none of these measures were related to pain intensity or CRPS severity, their clinical relevance is unclear.

Another strength of our study is that we controlled for potential response biases, which might have contributed to seemingly significant biases in previous TOJ studies. We also accounted for the fact that spatial attention might not normally be evenly distributed across space (see pseudoneglect, Jewell & McCourt, 2000) by obtaining comparative data from pain-free individuals. Follow-up Bayesian analyses showed anecdotal-to-moderate evidence of no differences between CRPS and pain-free participants on the visuospatial tasks (see also confidence intervals in Figure 2 illustrating no deviation from zero).

Nonetheless, although we aimed to create a diverse battery of tests of spatial cognition, there are three limitations that might have prevented us from detecting previously-reported spatial biases in our participants with CRPS. First, we were unable to include measures of tactile attention or egocentric reference frame, two measures upon which biased performance has been previously reported in CRPS (Moseley et al., 2009, 2012; Reid et al., 2016; Reinersmann et al., 2012; Sumitani, Shibata, et al., 2007; Uematsu et al., 2009). This is because we designed our protocol such that it only required transportable equipment and thus could be administered at patients' homes and in different research centres, in order to obtain large and representative sample. Second, most of our tasks did not involve body-relevant information, although it has been proposed that this might be critical for the manifestation of spatial biases in CRPS (Reid et al., 2016). The exception is our motor task, which by definition involves the body, and which revealed very little evidence of any systematic spatial deficits. Considering the above-mentioned limitations, we cannot rule out the possibility that our participants with CRPS might have presented with deficits in other domains of spatial cognition than those assessed in our study. Third, fatigue due to long and cognitively demanding assessments and / or pain medication acting on the central nervous system could potentially affect our participants' performance on the experimental tasks. For instance, these factors could be related to global detriment of attentional capacity and processing speed, leading to greater variability and cases of more extreme spatial biases in either direction among participants with CRPS compared to pain-free controls. Fatigue and medication could be also associated with decrease in psychomotor speed, potentially contributing to overall slowing of movements discussed in section 4.4. Notably, over half of the CRPS sample reported using opioid analgesics, which are often associated with subjective

experience of sedation or mental dullness. However, two systematic reviews of studies on the cognitive effects of opioid analgesia for chronic pain concluded that there is no evidence of significant detrimental effects on cognition (Ersek et al., 2004; Kendall et al., 2010). While some observational studies reported impaired processing and psychomotor speed and attention in patients with chronic pain treated with opioids, controlled studies rated as having higher quality showed either no effects of opioids on these cognitive functions, or some improvement. In fact, lower doses of opioids were associated with greater cognitive impairment (Kurita et al., 2012), while pain relief correlated with cognitive improvement (Byas-Smith et al., 2005; Sjøgren et al., 2000, 2005), suggesting that adequate analgesia might improve cognition by means of reducing pain. Therefore, possible cognitive side effects of pain medication cannot fully explain greater variability in cognitive performance and psychomotor slowing in our participants with CRPS compared to healthy controls.

Another limitation to the extent to which our results can be compared to those of previous studies that reported changes in spatial cognition in CRPS is that the duration of CRPS in our sample was on average longer (except when compared to Bultitude et al., 2017; 4 years vs. <1-3 years, Filbrich et al., 2017; Moseley et al., 2012, 2009; Reid et al., 2018, 2016; Sumitani et al., 2014). However, several arguments suggest that changes in spatial cognition should not become *less* apparent over time: (a) there are clinical indications of greater contribution of central mechanisms to the manifestation of CRPS in its more chronic stages (Birklein & Schlereth, 2015; Bruehl & Chung, 2015; Veldman et al., 1993); (b) we found that longer CRPS duration predicted bilateral slowing of movement initiation, which could reflect central changes in motor circuits; (c) there is evidence of positive correlations between CRPS duration and the extent of body perception distortion, body-related visuospatial bias, and spatially-defined motor bias (Lewis & Schweinhardt, 2012; Moseley, 2004; Reid et al., 2016, 2018); and (d) other studies (Bultitude et al., 2017; Filbrich et al., 2017; Frettlöh et al., 2006; Michal et al., 2016; Reid et al., 2016; Reinersmann et al., 2012) found no relationship between CRPS chronicity and any biases in spatial cognition, including our own findings from spatial tasks (Pearson's *rs* = 0.06 to 0.27; see Supplementary Figure S2). Another factor that could limit the extent to which our findings are comparable to previous experimental studies on spatial cognition in CRPS is that pain intensity reported by our participants was on average greater (except when compared to Bultitude et al., 2017, and Sumitani et al., 2014; 5.8/10 vs. 4.3-4.8/10, Filbrich et al., 2017; Moseley et al., 2012, 2009; Reid et al., 2018). However, previous research reported either positive relationships between pain intensity and severity of "neglect-like" symptoms (Frettlöh et al., 2006; Reid et al., 2016; Wittayer et al., 2018), or found no relationships between these factors (Bultitude et al., 2017; Filbrich et al., 2017; Michal et al., 2016; Moseley et al., 2009; Reid et al., 2016), including our own results (Pearson's *rs* = -0.12 to 0.20; see Supplementary Figure S2). Therefore, it is unlikely that the longer average disease duration or greater average pain intensity in our sample compared to previous research prevented us from detecting any impairments in spatial cognition.

5. Conclusions

Overall, the present findings suggest that unilateral upper-limb CRPS does not disrupt visual attention, mental representations, or motor function in a spatially-defined manner, and thus counter the analogy between CRPS and hemispatial neglect after brain injury. There were no behavioural indications of central changes in brain networks governing spatial cognition, suggesting that these are unlikely to be involved in the central mechanisms of CRPS. While bilateral slowing of movements could imply impairment of central mechanisms of motor control, it might simply reflect psychomotor slowing associated with chronic pain. Motor function appears to be related to some of the clinical features of CRPS rather than any spatial biases, although the extent of distorted cognitive representation of the affected limb seems to play a role in movement initiation speed and pain severity. These results support the promotion of treatments that aim to normalize body perception and improve motor function.

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Chapter 4 - Conclusions

This study used a series of experimental measures to examine whether people with CRPS present with perceptual, representational, and motor "neglect-like" deficits, compared to pain-free individuals. However, I found no evidence of altered attention to and representation of the CRPS-affected side of space, nor any systematic slowing of movements directed towards the affected relative to unaffected side. Furthermore, the extent of any changes in spatial cognition was not related to the severity of pain or other symptoms of CRPS. Instead, motor function and body representation appear to be associated with severity of pain and other symptoms. These findings question the presence and clinical relevance of "neglect-like" neuropsychological changes in CRPS, thus challenging the involvement of cortical reorganisation in the manifestation of the disorder.

To place the findings of this chapter within the context of the rest of the thesis, this study did not replicate "neglect-like" deficits in CRPS while controlling for potential response biases, such as those reported in Chapter 2. This could suggest that some of the previously found deficits in spatial attention might be explained by participants' decisional bias for reporting the stimuli on their unaffected side. Furthermore, in this study I aimed to test "pure" spatial biases and avoid potential overlap with distorted representation of the CRPS-affected limb. However, the "somatospatial inattention" hypothesis (Reid et al., 2016) discussed in Chapter 1 would suggest that spatial biases could be exacerbated in the presence of body-related information. Thus, the magnitude of any biases in this study could be too small to demonstrate any significant deviations from normal. However, the case study in Chapter 2 and one previous group study (Bultitude et al., 2017) demonstrated significant biases away from the affected side using the same experimental setup excluding body-relevant information. Therefore, it is unlikely that the specific task procedure would prevent the detection of any existing spatial bias. In the context of potential dissociations between biases in distinct domains of spatial cognition discussed in Chapters 1 and 2, the findings described in this chapter were consistent across all measures of visuospatial cognition in near space and mental representation of space, suggesting that overall, people with CRPS did not present with lateralised deficits in spatial cognition.

In addition to perceptual and representational signs of neglect, this study also tested for directional motor neglect, adding to the scant literature regarding movement related spatial biases discussed in Chapter 1. Although previous studies have tested for spatial motor biases in CRPS in the form of speed and accuracy of movements with either hand performed in the affected versus unaffected side of space, as well as a self-reported questionnaire, none had examined directional motor neglect (that is, slowing of movements directed towards the affected relative to unaffected side of space). While I found no systematic evidence of spatially-defined deficits on the motor task, participants with CRPS were generally slower than pain-free controls to initiate and execute

movements regardless of which hand they used. This deficit could not be explained by motor neglect, primary motor signs of CRPS, or learned underutilisation of the painful limb. Instead, slowing of movements affecting both limbs could be considered a sign of functional reorganisation in central motor networks, consistent with the conclusions from several previous behavioural and neuroimaging studies (Juottonen et al., 2002; Maihofner et al., 2007; Ribbers et al., 2002; Schilder et al., 2012; Schwenkreis et al., 2003). However, it also appears consistent with the impairment of psychomotor speed that is common in chronic pain more generally (Higgins et al., 2018). Overall, lack of any perceptual, representational, and motor spatial biases in the current study challenges the analogy between hemispatial neglect after brain injury and CRPS. Although central mechanisms of CRPS are thought to involve functional cortical reorganisation (Kuttikat et al., 2016; Reinersmann, Maier, et al., 2013), my behavioural findings suggest that such reorganisation, at least in the parietal cortical networks involved in spatial cognition, is unlikely.

While recognising overall unbiased spatial cognition, the individual variability in the performance of participants with CRPS illustrated in this chapter has other theoretical implications. First, it could explain why the overall results of this study are not consistent with the findings from the case study reported in Chapter 2. That is, individual neuropsychological abnormalities can be easily lost in large group studies, due to the heterogeneity of CRPS (Caramazza, 1986). Second, the results presented in this chapter suggest greater than previously assumed variability in the direction of any spatial biases. Specifically, some participants showed biases towards their affected side, contrary to the hypothesised "neglect-like" bias. In fact, there are only two reported cases, including the one described in Chapter 2, of spatial biases towards the CRPS-affected side on measures similar to those reported in this chapter (Christophe, Delporte, et al., 2016; Jacquin-Courtois et al., 2017). Using a different measure, studies from one research group suggest a deviation in the egocentric reference frame towards the CRPS-affected side (Sumitani et al., 2014; Sumitani, Rossetti, et al., 2007; Sumitani, Shibata, et al., 2007; Uematsu et al., 2009). Therefore, the inconsistencies in the direction of spatial biases discussed in Chapter 1 could be partly due to specific characteristics of CRPS participants available in particular research centres, or simply reflect chance findings. If there are any changes in spatial cognition, these might be more variable in broader CRPS population.

Although on average participants with CRPS did not show any spatial biases, individual variability in their performance could still theoretically reveal some relationships between these biases and clinical symptoms of CRPS (for example, if spatial bias only significantly contributed to pathology for a subgroup of patients). However, exploratory analyses showed no such associations in this study, therefore questioning the clinical relevance of any changes in spatial cognition. Instead, the results indicated a potential role of self-reported body representation and motor function in clinical manifestation of CRPS, with greater motor deficits in more chronic stages of the disorder. These preliminary findings highlight the key role of motor impairment in

the maintenance and severity of CRPS symptoms. While recognising the importance of using the affected limb, they also suggest that not all deficits might be overcome by physical exercise and multidisciplinary treatment should also address body perception and adequate pain control.

Null results regarding the presence and clinical relevance of lateralised biases in spatial cognition in this study might have implications for the effects of prism adaptation tested in Chapter 5. If prism adaptation reduces pain through normalising spatial attention, it might not incur the expected benefits for participants who do not show the hypothesised neglect for their affected side. However, the findings reported in this chapter demonstrate substantial individual variability among participants with CRPS in their performance on the tests of spatial cognition and motor function. Namely, looking at the individual data, there were subgroups of participants who presented with biases away from, or towards their affected side on different tasks, in addition to those whose performance did not differ from pain-free controls. Thus, prism adaptation might still reduce pain through an attentional mechanism for the subgroup of participants with deficits in attention to their affected side at baseline.

Yet presence of participants who showed a bias towards their affected side (opposite to "neglect-like" deficit) has further implications for the applicability of the protocol of prism adaptation treatment proposed in Chapter 3. Participants allocated to the prism adaptation treatment arm are exposed to a uniform direction of visual shift, that is, away from their CRPS-affected side, so that the adaptation leads to after-effects towards their affected side. If this intervention aims to normalise baseline spatial bias, it could be argued that individuals showing a bias toward their affected side should perform the treatment using prism lenses that shift the visual image towards their affected side, and thus adapt in the opposite direction. However, participants in the first study of prism adaptation in CRPS (Sumitani, Rossetti, et al., 2007) showed baseline spatial shift of their egocentric reference frame towards the affected side, yet their pain decreased following prism adaptation in the direction that would induce after-effects towards their affected side. When one of these participants later underwent adaptation in the opposite direction, her pain increased. Therefore, there is currently insufficient evidence to support prescribing the direction of prismatic shift based on individual direction of baseline spatial bias. First, we should gain better understanding of the mechanisms of prism adaptation in CRPS. Among other things, in Chapter 5 I will be able to test whether any benefit of prism adaptation is specific to those patients who show a bias away from their affected side. If so, then this could support further investigations to test whether patients with the opposite baseline bias benefit from adaptation to prismatic shifts in the opposite direction.

Even though the majority of tested participants with CRPS showed balanced spatial performance, therapeutic benefits of prism adaptation might still be achieved through some mechanisms other than correcting spatial bias, such as normalising sensory-motor integration. This alternative mechanism relies on a hypothesis that distorted representation of the affected limb gives rise to

incongruencies between predicted and actual consequences of movement. Such sensory-motor conflicts are thought to contribute to pathological pain, including CRPS (Brun et al., 2019; Harris, 1999; McCabe & Blake, 2008). Higher subjective disturbance of body perception among participants with CRPS described in this chapter compared to pain-free individuals, and its predictive value for pain severity, would support this potential mechanism. In Chapter 5 I will report more objective, experimental assessment of cognitive representation of the affected limb, and investigate both proposed mechanisms of prism adaptation and whether any individual differences in baseline spatial or body representation biases are related to changes in pain and CRPS symptom severity. Although the findings reported in the current chapter challenge the primary rationale for using prism adaptation as a potential treatment for CRPS, this intervention might still bring therapeutic effects though different mechanisms, and / or for a subset of individuals with CRPS.

Chapter 5: Prism adaptation treatment for upper-limb Complex Regional Pain Syndrome: a double-blind randomized controlled trial

Chapter 5 – Introduction

In this final chapter, I will present the findings from a randomised controlled trial of prism adaptation for CRPS, the protocol of which was described in Chapter 3. This treatment is thought to reduce pain and other CRPS symptoms (Bultitude & Rafal, 2010; Christophe, Chabanat, et al., 2016; Sumitani, Rossetti, et al., 2007) by increasing attention to the affected side, consistent with its primary application in rehabilitation of hemispatial neglect (Rossetti et al., 1998). However, I also consider a second possible mechanism, based on normalising body representation and correcting sensory-motor incongruence. The key research question that has not been addressed thus far is whether prism adaptation can reduce pain and CRPS severity more than a control treatment. Since the mechanisms through which prism adaptation can relieve pain are still unclear, I will also report how it affects a range of secondary outcomes, including neuropsychological functions relevant to prism adaptation such as spatial cognition and body representation. Prism adaptation is expected to lead to greater reductions in neuropsychological symptoms, clinical signs of CRPS, and self-reported CRPS-related and psychological disturbances, compared to control treatment. To assess any fluctuations in the outcomes of interest, participants undergo two baseline assessments, one month apart. Participants' performance in the first baseline session, compared to pain-free controls, was examined in Chapter 4 to address research questions separate from the main objective of this trial. The second baseline session takes place immediately before commencing two weeks of prism adaptation or sham treatment. The effects of these treatments on the primary and secondary outcomes are assessed immediately after completing the treatment. To examine how long any benefits of treatment are sustained for, participants are assessed again one month later, and a subset of self-reported outcomes is also collected three and six months after completing the treatment. Finally, in this chapter I explore any baseline characteristics of participants with CRPS that could predict how much their pain and symptom severity improve or deteriorate over time. I discuss the findings in the context of previous studies on prism adaptation, characteristics of our sample, specific features of the two treatment arms, different proposed mechanisms of prism adaptation, and relationships between clinical and neuropsychological symptoms.

Similar to the procedures used in the previous studies of prism adaptation for post-stroke hemispatial neglect and CRPS, participants in this trial undergo two weeks of twice-daily prism adaptation treatment, performed using the affected limb, with prismatic lenses shifting visual image approximately 19° away from the affected side to obtain after-effects towards the affected

side. The major differences between this and previous studies on CRPS are (a) the random allocation of participants to either prism adaptation, or control treatment of the same intensity and duration, which uses neutral lenses that do not shift the visual image and thus the training does not induce any adaptation; (b) the blinding of the participants and the researcher to treatment allocation; and (c) the sample of participants allocated to prism adaptation treatment being three times greater than the largest sample of existing studies (Christophe, Chabanat, et al., 2016). Overall, this chapter presents a robust, well-controlled, and unbiased assessment of prism adaptation treatment for CRPS, substantially improving upon the preliminary studies.

Statement of authorship

This declaration concerns the article entitled:			
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Copyright status (tick the appropriate statement) I hold the copyright for this material [x] Copyright is retained by the publisher, but I have been given permission to replicate the material here [ ]			
Candidate's contribution to the paper (provide details, and also indicate as a percentage)	Monika Halicka considerably contributed to this study (80%), being involved in formulation of ideas (65%), design of methodology (70%), experimental work (95%), and presentation of data in journal format (95%).		
Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.		
Signed	Monika Halicka	**Date**	10.05.2020

Chapter 5

Prism adaptation treatment for upper-limb Complex Regional Pain Syndrome: a double-blind randomized controlled trial

Halicka, Monika[a,b]*; Vittersø, Axel D.[a,b,c]; McCullough, Hayley[d]; Goebel, Andreas[d,e]; Heelas, Leila[f]; Proulx, Michael J.[b,g]; Bultitude, Janet H.[a,b]

[a]Centre for Pain Research, University of Bath, Bath, United Kingdom

[b]Department of Psychology, University of Bath, Bath, United Kingdom

[c]Department of Sport and Health Sciences, University of Exeter, Exeter, United Kingdom

[d]Pain Research Institute, Department of Translational Medicine, University of Liverpool, Liverpool, United Kingdom

[e]Department of Pain Medicine, Walton Centre NHS Foundation Trust, Liverpool, United Kingdom

[f]Optimise Pain Rehabilitation Unit, Oxford University Hospitals NHS Trust, Oxford, United Kingdom

[g]Centre for Reality & Virtual Environments Augmentation Labs, Department of Computer Science, University of Bath, Bath, United Kingdom

*Corresponding author

Email: mon.halicka@gmail.com

Phone: +44 1225 386226

Address: Department of Psychology, 10 West, University of Bath, Claverton Down, Bath, BA2 7AY, United Kingdom

URL: https://www.bath.ac.uk/research-centres/centre-for-pain-research-cpr/

Abstract

Initial evidence suggested that people with Complex Regional Pain Syndrome (CRPS) have reduced attention to the affected side of their body and the surrounding space, which might be related to pain and other clinical symptoms. Three previous unblinded, uncontrolled studies showed pain relief following treatment with prism adaptation, an intervention that has been used to counter lateralised attention bias in brain-lesioned patients. To provide a robust test of its effectiveness for CRPS, we conducted a double-blind randomized controlled trial of prism adaptation for unilateral upper-limb CRPS-I. Forty-nine eligible adults with CRPS were randomized to undergo two-weeks of twice-daily home-based prism adaptation treatment (n = 23) or sham treatment (n = 26). Outcomes were assessed in person four weeks prior to and immediately before treatment, and immediately after and four weeks post-treatment. Long-term postal follow-ups were conducted three and six months after treatment. We examined the effects of prism adaptation versus sham treatment on current pain intensity and CRPS symptom severity score (primary outcomes); as well as sensory, motor, and autonomic functions, self-reported psychological functioning, and experimentally tested neuropsychological functions (secondary outcomes). Primary and secondary outcomes did not differ between the prism adaptation and sham treatment groups when tested at either time point following treatment. Overall, CRPS severity significantly decreased over time for both groups, but we found no benefits of prism adaptation beyond sham treatment. Our findings do not support the efficacy of prism adaptation treatment for relieving upper-limb CRPS-I. This trial was prospectively registered (ISRCTN46828292).

Keywords

Complex Regional Pain Syndrome; Prism adaptation; Randomized controlled trial; Attention; Pain; CRPS symptom severity; Body representation; Neuropsychology; Neglect

1. Introduction

Complex Regional Pain Syndrome (CRPS) is associated with continuous pain in one or more limbs accompanied by sensory, motor, and autonomic disturbances that are disproportionate to any inciting injury [34]. Individuals with CRPS can also show neuropsychological symptoms reminiscent of hemispatial neglect after brain injury [32] (see Chapter 1). These can present as distorted cognitive representations of the CRPS-affected limb(s) [44,51,74,90,99], reduced attention to the affected limb(s) and corresponding side of external space [12,21,24,26,78,89], poorer mental representation of the affected side of space [104], and spatially-defined motor deficits [89]. The extent of these neuropsychological changes has been associated with the severity of clinical signs of CRPS [24,46,51,77,78,89,90,113] and could pertain to its central mechanisms [91].

Prism adaptation (PA) is a sensorimotor training technique used to reduce lateralised biases in attention, spatial representations, and (ocular)motor performance in hemispatial neglect after brain injury [56,70,95]. Considering similar deficits in CRPS, three previous studies tested the efficacy of PA in a total of 13 patients with this condition. They reported significant relief of pain and other CRPS symptoms following eight to 20 PA sessions performed with the affected arm when participants adapted towards their affected side [10,13,105]. The reduction in pain lasted up to two weeks. Thus, PA has the potential to durably relieve pain and other symptoms of CRPS. Because PA is quick (5-10 minutes a day), inexpensive, and self-administered, it is an appealing intervention compared to more intensive neurocognitive treatments like graded motor imagery [75]. However, the strength of available evidence for PA is limited, because it was only previously tested in small samples, without any control treatments or blinding.

The mechanisms through which PA could relieve pain are unclear. One possibility is that it increases attention to the CRPS-affected side relative to the unaffected side. Indeed, when one patient underwent adaptation in the opposite direction such that the theoretical attention bias away from the affected side would be exacerbated, their pain increased [105]. More severe self-reported "neglect-like" symptoms and spatial attention and motor biases have been related to greater pain intensity and worse long-term pain outcomes [24,89,90,113]. A potential second mechanism is that PA restores normal sensorimotor integration, the disruption of which is thought to contribute to pathological pain including CRPS [9,37,64,105]. This is consistent with the findings that individuals without spatial biases can also benefit from PA [13].

Despite promising preliminary evidence, no studies have attempted a robust test of the effects of PA on CRPS. Therefore, we conducted a double-blind, randomized, sham-controlled trial of PA for upper-limb CRPS-I. We hypothesised that two weeks of twice-daily PA treatment would reduce the primary outcomes of pain intensity and CRPS symptom severity more than sham treatment of the same intensity. We also predicted greater reductions in the secondary outcomes

of neuropsychological symptoms (i.e. biases in spatial cognition, motor control, and body representation), clinical signs of CRPS, and self-reported CRPS-related and psychological disturbances following PA compared to sham treatment. The outcomes were assessed at six time points: to establish a one-month pre-treatment baseline, and to examine any immediate effects of PA and their retention at one, three, and six months post-treatment.

2. Methods

2.1. Study design and participants

The study was a two-arm parallel group RCT. It was prospectively registered (ISRCTN46828292) and the full details of the study are reported in the study protocol and analysis plan [33] (see Chapter 3). Any protocol deviations are specified in Text S1, Supplemental Material. The study was approved by the UK National Health Service (NHS) Oxfordshire Research Ethics Committee A and Health Research Authority (REC reference 12/SC/0557).

Recruitment was conducted via post and clinicians' referrals through the National CRPS-UK Registry, internal registries of the Royal United Hospitals and Walton Centre NHS Foundation Trusts, and clinicians' referrals through the Oxford University Hospitals NHS Foundation Trust and other NHS pain clinics in the UK. Word of mouth, print and online advertisements, as well as social media were further used to disseminate information about the study. Participants were recruited between March 2017 and December 2018, and the final long-term follow-up took place in July 2019.

Following provisional assessment of eligibility through a phone interview, recruited participants took part in four research sessions (RS) at the University of Bath (n = 33), University of Liverpool (n = 9), or in the participant's home (for participants who were unable to travel; n = 7). Participants gave written informed consent at the beginning of RS1, prior to any study-related procedures. The research sessions involved in-person assessment of eligibility criteria and of the primary and secondary outcomes, including self-report questionnaires, clinical assessments, and tests of neuropsychological functions. Each RS lasted from two to four hours, including breaks between the assessments. The data collection schedule is presented in Figure 1. The baseline was measured over two research sessions (RS1 and RS2) separated by four weeks. Immediately after RS2, participants commenced a two-week home-based treatment period. Treatment outcomes were measured over two research sessions, one immediately (RS3) and one four weeks (RS4) after completing the treatment. Two long-term follow-ups were conducted via post – one at 12 weeks (LTFU1) and one at 24 weeks (LTFU2) after completing the treatment. The flow of participants through each stage of the study is displayed in a CONSORT diagram (Figure 2).

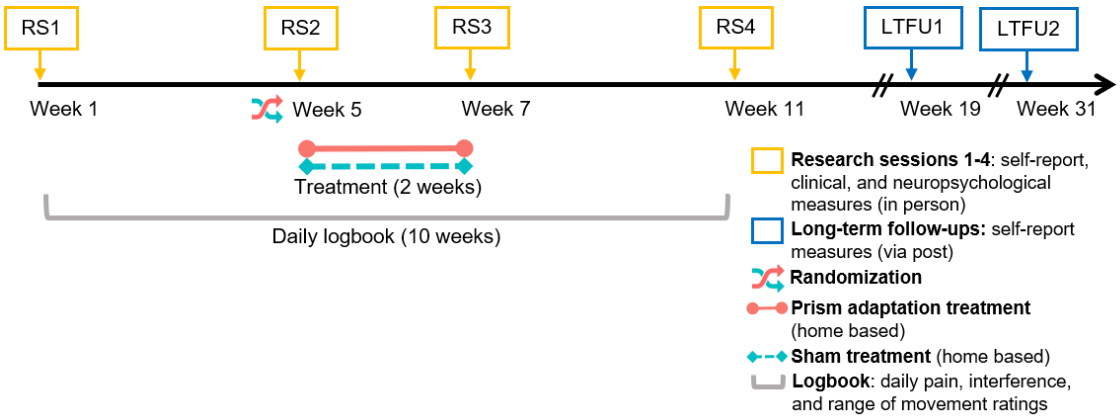

Figure 1. Schedule of data collection and interventions.

Participant inclusion criteria were: being aged 18-80 years; having a diagnosis of CRPS-I primarily affecting one upper limb based on the Budapest research criteria [34]; having a CRPS diagnosis for ≥3 months at the time of RS1; and having a current pain intensity ≥2 on a 0-10 Numeric Rating Scale. Exclusion criteria were: lacking sufficient English language ability to provide informed consent; being classified as legally blind; reporting a history of neurological disorder (e.g. stroke, neurodegenerative disease, or traumatic brain injury); having CRPS in the opposite limb meeting the Budapest clinical or research criteria; reporting confirmed nerve damage (CRPS-II); reporting or showing dystonia or other physical impairment that would prevent satisfactory execution of PA/sham treatment; or reporting severe psychiatric comorbidity (e.g. schizophrenia [109]) that could be associated with perceptual changes. Inclusion and exclusion criteria were assessed in RS1 and RS2.

Participants were primarily recruited for the current RCT of PA treatment, but we also collected measures of spatial cognition, motor control, and body representation at baseline (RS1) for comparison with pain-free controls (data reported elsewhere [31], Chapter 4).

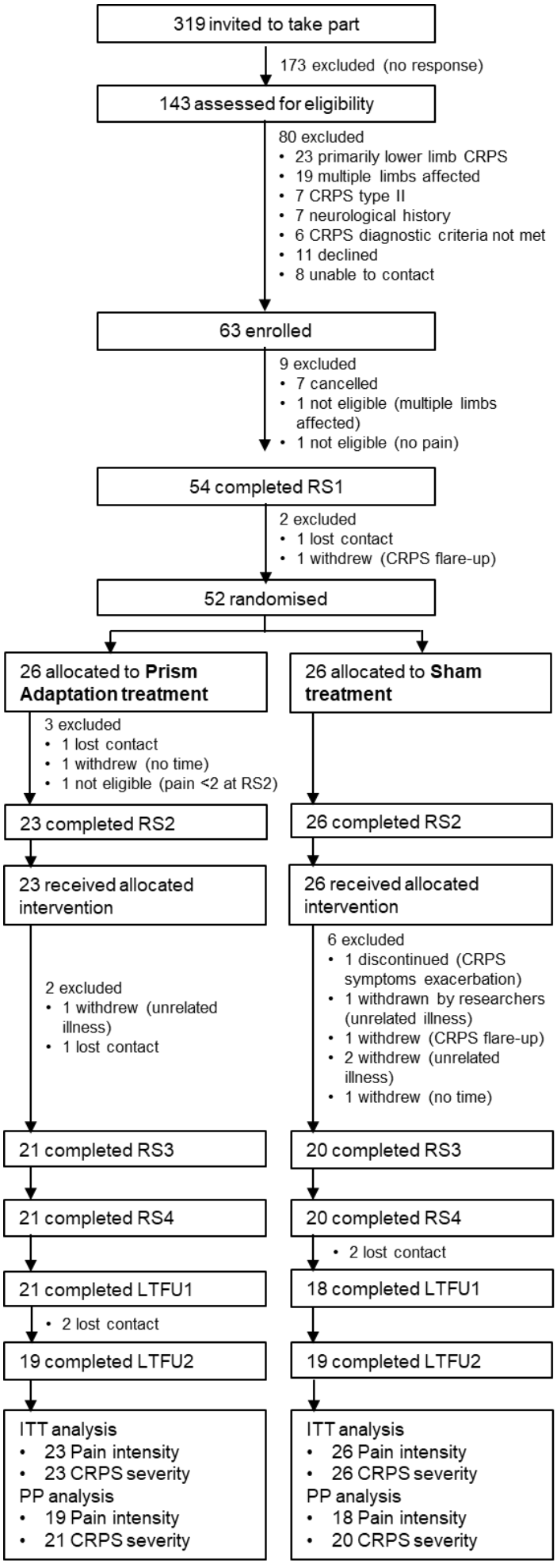
319 invited to take part
173 excluded (no response)
143 assessed for eligibility
80 excluded
• 23 primarily lower limb CRPS
• 19 multiple limbs affected
• 7 CRPS type II
• 7 neurological history
• 6 CRPS diagnostic criteria not met
• 11 declined
• 8 unable to contact
63 enrolled
9 excluded
• 7 cancelled
• 1 not eligible (multiple limbs affected)
• 1 not eligible (no pain)
54 completed RS1
2 excluded
• 1 lost contact
• 1 withdrew (CRPS flare-up)
52 randomised
26 allocated to Prism Adaptation treatment
26 allocated to Sham treatment
3 excluded
• 1 lost contact
• 1 withdrew (no time)
• 1 not eligible (pain <2 at RS2)
23 completed RS2
26 completed RS2
23 received allocated intervention
26 received allocated intervention
2 excluded
• 1 withdrew (unrelated illness)
• 1 lost contact
6 excluded
• 1 discontinued (CRPS symptoms exacerbation)
• 1 withdrawn by researchers (unrelated illness)
• 1 withdrew (CRPS flare-up)
• 2 withdrew (unrelated illness)
• 1 withdrew (no time)
21 completed RS3
20 completed RS3
21 completed RS4
20 completed RS4
• 2 lost contact
21 completed LTFU1
18 completed LTFU1
• 2 lost contact
19 completed LTFU2
19 completed LTFU2
ITT analysis
• 23 Pain intensity
• 23 CRPS severity
PP analysis
• 19 Pain intensity
• 21 CRPS severity
ITT analysis
• 26 Pain intensity
• 26 CRPS severity
PP analysis
• 18 Pain intensity
• 20 CRPS severity

Figure 2. CONSORT diagram. Flow of participants through the study. RS1, research session 1; RS2, research session 2; RS3, research session 3; RS4, research session 4; LTFU1, long-term follow-up 1; LTFU2, long-term follow-up 2; ITT, intention-to-treat analysis (received allocated intervention); PP, per-protocol analysis (completed allocated intervention, RS3-4 [CRPS severity], and LTFU1-2 [Pain intensity]).

2.2. Interventions

Both groups were instructed to continue any usual treatments (including medications) but were asked not to change their treatment regimens throughout the duration of the trial if possible. Current treatments and any changes are reported in Table S1, Supplemental Material.

2.2.1. Prism adaptation treatment

Participants randomised to the PA treatment used welding goggles fitted with 35-diopter Fresnel lenses that induced approximately 19° lateral optical deviation (visual shift) away from the CRPS-affected side. In each treatment session, participants were seated approximately 50cm from a wall or other vertical surface (distance was adjusted individually to correspond to the participant's almost fully extended arm). An A4 sheet was positioned on the wall in a landscape orientation at eye-level and in line with their body midline. There were two targets (2cm-diameter red circles) on the pointing sheet, located 12.5cm to the left and 12.5cm to the right of participant's body midline. While wearing the prism goggles, participants used their CRPS-affected arm to perform 50 pointing movements, as fast as possible, alternating between the left and right target.

An example of prism adaptation is illustrated in Figure 3. Prismatic shifts were directed away from the CRPS-affected side, thus participants with left-CRPS would use rightward-shifting prism goggles as illustrated in the figure. Due to the rightward visual shift, pointing would initially err to the right. However, with repeated movement execution and motor learning, the pointing would become increasingly accurate, as the movements would adjust in the opposite direction (to the left). This adaptive realignment of sensorimotor reference frames [87,107] would produce movement after-effects towards the left (affected) side. That is, once the goggles were removed, pointing would temporarily err to the left. Conversely, participants with right-CRPS would use leftward-shifting prismatic goggles to induce adaptive realignment (movement after-effects) towards their affected side. Studies from neurologically healthy individuals and stroke patients show that these short-term movement after-effects are accompanied by a longer-lasting realignment of attention, spatial representations, and lateralised (ocular)motor performance in the same direction as the after-effect [4,15,23,42,47,54–56,66,67,70,94,95,100,101,103,111].

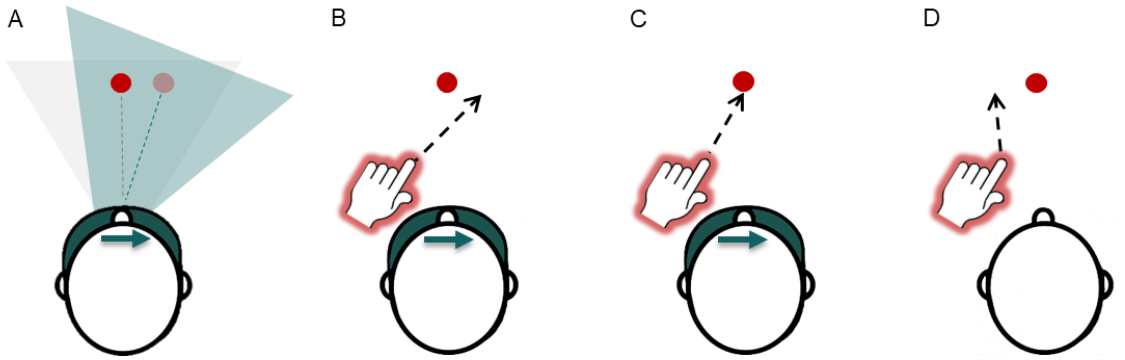

Figure 3. Prism adaptation procedure. In this example, participant with left-CRPS is using rightward-shifting prisms (A-C), which induce adaptation towards the left (affected) side. For clarity of illustration, only one target (red circle) is represented in the figure. However, the treatment procedure involved two targets presented in the left and right side of space, and participants' pointing movements alternated between the left and right targets. (A) Prism goggles shift visual image to the right. Blue triangle represents a shift of visual perspective and perceived target location (pale red circle), relative to real location of the target (light grey triangle, dark red circle). (B) Pointing movements initially err to the right. (C) Adaptive realignment results in correct pointing movements. (D) Goggles are removed and pointing movements err to the left (after-effect).

The chosen direction of PA, inducing a visual shift away from the affected side and thereby an after-effect towards the affected side, is consistent with previous CRPS studies [10,13,105] and the technique's application in rehabilitation of hemispatial neglect after brain injury [56,95]. To enhance the effects of PA, welding goggles occluded the first half of the arm movement and participants were encouraged to point as quickly as possible. Both these measures are thought to reduce any deliberate misaiming on behalf of the participants and encourage greater adaptive realignment (i.e. "true" sensorimotor adaptation) [19,87,88].

Immediately after RS2, participants were trained in person in how to carry out the treatment by a research psychologist JHB or ADV (neither of whom were involved in any data collection) according to a standardised protocol (see training script in Text S2, Supplemental Material). Once the researcher was satisfied that the participant understood the treatment procedure, they performed the first treatment during this training session under the guidance of the researcher. At the end of the training session participants received a pair of prism goggles in a sealed opaque bag, a pointing sheet, written instructions, and a link to a video tutorial (see Video S1, https://youtu.be/dcLuyPfFowM) to take home. In addition to the treatment that they underwent during training, participants were instructed to perform twice-daily self-guided treatment sessions at home for two weeks, resulting in 29 treatment sessions in total. Participants were instructed to commence the home-based treatment on the day following RS2, perform one session in the morning and one in the evening, and record the start and end time of each session in a provided logbook.

2.2.2. Sham treatment

Participants randomized to the sham treatment carried out exactly the same procedure as described above, except they used welding goggles fitted with neutral lenses that did not induce any lateral visual shift [11,70]. The neutral lenses distorted the acuity and clarity of vision to a similar extent as prism lenses (only without any lateral shift), therefore the two treatment arms were similar aside from the sensorimotor adaptation.

2.3. Randomisation and blinding

Participant randomization was performed 1-5 days before RS2 by JHB, who was not involved in any data collection. Participants were randomly assigned to either PA or sham treatment group with equal allocation ratio, using MINIM [69] software to minimize baseline (RS1) group differences in current pain intensity, CRPS severity score, primarily affected arm, pre-CRPS dominant hand, sex, age, presence of CRPS in other body parts, presence of other non-CRPS pain, and CRPS duration. The primary outcome measures (current pain intensity and CRPS severity score) were given double weighting compared to the other minimisation characteristics as we considered matching the two groups for these factors to be a higher priority. Minimisation ensures balance between groups across multiple factors, even in small samples. While the first participant is allocated using simple randomisation, the treatment allocated to the subsequent participants partly depends on the characteristics of those participants already allocated [1,108]. Note that participants excluded between treatment allocation and completion of RS3 (Figure 2) were removed from the minimisation procedure so that subsequently recruited participants could be allocated independent of these exclusions and according to the current pool of participants remaining in each arm.

The only researchers who were aware of individual treatment allocations were those who randomised the participants and/or trained them in carrying out PA or sham treatments and provided them with prism or neutral goggles (JHB and/or ADV). These researchers were not involved in the assessments of any outcomes at any point in the trial. In RS3, the participants returned the goggles in a sealed opaque bag to MH, which she handed unopened to JHB. The researcher responsible for enrolment and all data collection (MH) remained blinded to participants' treatment allocation until the last participant completed their RS4. Following RS4, there were no further in-person assessments as the long-term follow-up was conducted via postal questionnaires and scored by blinded research assistants. The participants were blinded to their treatment allocations throughout the entire duration of the trial. They were informed that they might receive real or sham treatment, and that both involved reaching out to touch visual targets with their affected arm while wearing goggles that distort vision. However, participants were not made aware of the specific nature of the intervention nor the differences between the types of

goggles used in the two treatment arms. All documentation and instructions referred to the treatment arm as "sensorimotor training".

2.4. Measures

2.4.1. Demographics

In RS1, participants reported on demographic characteristics, including age, sex, and handedness prior to CRPS onset. They were asked to complete two versions of Edinburgh Handedness Inventory (EHI) [81]: once rating their recalled hand preference prior to CRPS onset, and once rating their current hand preference. Total scores can range from -100 (extreme left-handedness) to 100 (extreme right-handedness). To approximate the functional impact of CRPS, we calculated an absolute difference between current and recalled EHI scores, that is, change in handedness. We also interviewed the participants regarding their clinical history, including the date and type of any inciting injury, CRPS duration (time since diagnosis), any co-morbidities, and any ongoing treatments for CRPS.

2.4.2. Primary outcomes

A change between RS2 and RS3 in current pain intensity and CRPS symptom severity score were the primary outcomes. In RS1-RS4 and LTFU1-LTFU2, participants rated their current pain intensity in the CRPS-affected limb on a Numerical Rating Scale (NRS) from 0 (no pain) to 10 (pain as bad as you can imagine). This measure was taken from the Brief Pain Inventory (BPI; item 6) [14] and has been recommended as a core outcome for chronic pain trials [17,30]. CRPS severity was assessed in RS1-RS4 according to a standardised protocol [36]. Eight self-reported symptoms and eight signs evaluated upon clinical examination were scored as 0 (absent) or 1 (present) based on sensory testing, and visual and manual examination (see section 2.4.3.2. for details). The summed CRPS severity score can range from 0 (no CRPS symptoms) to 16 (most severe CRPS symptoms). The CRPS severity score has good discrimination abilities, concurrent validity, and adequate sensitivity to change [35,36], and was recommended as the core outcome measure for CRPS clinical studies [30].

2.4.3. Secondary outcomes

2.4.3.1. Self-report measures

Self-reported secondary outcomes measured in RS1-RS4 and LTFU1-LTFU2 included questionnaires about pain, body representation, and emotional functioning. We measured pain intensity and interference, using the BPI (0-10 scale for each subscale; higher scores indicate greater intensity/interference [14]), and neuropathic features of experienced pain, using Pain Detect Questionnaire (PDQ; -1-38 scale; higher scores indicate greater neuropathic component of pain [25]). Body representation was measured using the Bath CRPS Body Perception Disturbance Scale (BPDS; 0-57 scale; higher scores indicate greater distortions of body perception [50]). For

emotional functioning, we measured pain-related fear of movement and re-injury, using Tampa Scale for Kinesiophobia (TSK; 17-68 scale; higher scores indicate more severe kinesiophobia [68]) and mood disturbance, using Profile of Mood States (POMS; 17-229 scale; higher scores indicate greater mood disturbance [65]). In RS1, participants also rated their levels of optimism and pessimism, using Revised Life Orientation Test (LOTR; 0-24 scale; higher scores indicate higher optimism level [98]), and their expectations and criteria for success in chronic pain treatment, using Patient Centred Outcomes Questionnaire (PCOQ; each item scored on 0-10 scale; higher scores indicate higher usual, desired, expected, and considered successful (in terms of the treatment outcome) levels of pain, fatigue, emotional distress, and interference, and higher importance of improvement in each of these areas [92]). In post-treatment RS3-RS4 and LTFU1-LTFU2, participants rated their impression of how much their activity limitations, symptoms, emotions, and overall quality of life related to CRPS changed due to treatment, using the Patient Global Impression of Change questionnaire (PGIC; 1-7 scale; 1 indicates no change or worsening of symptoms; higher scores indicate greater improvement [39]). We chose the abovementioned self-report questionnaires based on recommendations for core outcome measures for chronic pain trials [17] and the existing literature on CRPS implicating other relevant measures (e.g. [29]). The LOTR and PCOQ were included to assess whether two treatment groups were matched on their average optimism and expectations of outcomes, because these factors can affect the success of novel treatments [5,52,110].

Throughout the first 10 weeks of the trial (RS1-RS4), participants rated their average level (over the past 24 hours) of pain intensity, the degree to which their symptoms interfered with their daily life, and range of movement in the affected limb, using daily logbooks (0-10 NRS scale; higher scores indicate greater pain intensity, symptoms interference, and better range of movement).

2.4.3.2. Clinical assessments

We assessed participants' CRPS signs and symptoms, and sensory, autonomic, and motor functions in RS1-RS4. Each assessment started with the unaffected side. Sensory tests were performed on the most painful site on the CRPS-affected limb and the corresponding site on the unaffected limb, unless specified otherwise.

2.4.3.2.1. CRPS diagnostic criteria and symptom severity score

The Budapest research criteria were assessed in RS1 and RS2 to confirm CRPS diagnosis, and in RS3 and RS4 to determine whether participants still met the diagnostic criteria post-treatment. The same assessments were used to calculate the CRPS severity score in each research session. Specifically, participants reported whether they experienced: (1) continuous, disproportionate pain in their affected limb; (2) allodynia, hyperpathia, and/or hypoesthesia in their affected limb; (3) temperature, (4) colour, and (5) sweating asymmetries between the affected and unaffected limbs; (6) oedema, (7) dystrophic changes, and (8) motor abnormalities in their affected limb. During each research session, we also tested for presence of the same CRPS signs: (9)

hyperalgesia, using a single pinprick; (10) allodynia, using a single brush stroke, touch of a 128Hz tuning fork, and of a cold metal pen; (11) temperature asymmetry, using an infrared thermometer (arithmetic mean of three recordings from each limb; asymmetry was present if absolute difference between two limbs was >1°C); (12) colour asymmetry, using visual examination; (13) asymmetric oedema, using a figure-of-eight hand size measure [83] (arithmetic mean of three measurements of each hand; oedema was present if size of the affected hand was >0.56cm larger than size of the unaffected hand [48]); (14) sweating asymmetry, using visual and tactile examination; (15) dystrophic changes, using visual examination; and (16) motor abnormalities, using an electronic hand dynamometer (arithmetic mean of three maximum force grips with each hand; weakness was present if affected/unaffected hand grip force ratio was <0.95 [left-handed participants] or <0.85 [right-handed participants] [41,84]), delta finger-to-palm distance [106] (ΔFTP; decreased range of movement was present if affected/unaffected ratio was <0.9), and visual examination (tremor, muscle spasms, dystonia, range of movement).

The reported symptoms, and the signs of CRPS rated as present upon in-person examination were summed to obtain the CRPS severity score. We additionally took photographs of both limbs and videos of fist closure and opening, wrist flexion, extension, and radial and ulnar deviation. These were double-scored for the presence of colour asymmetry, dystrophic changes, and motor abnormalities by a trained research assistant who was blind to treatment allocation, affected limb, and time point of assessment. Cohen's kappa statistics for inter-rater agreement were significantly different from zero, indicating fair agreement for colour asymmetry (κ = .21, p = .004) and dystrophic changes (κ = .23, p < .001), and borderline slight/fair agreement for motor impairment (κ = .20, p < .001).

2.4.3.2.2. Sensory, autonomic, and motor signs of CRPS

Secondary outcomes of sensory function of the affected relative to unaffected limb assessed in RS1-RS4 included elements of quantitative sensory testing, administered according to the standardised protocol [93]. Specifically, we measured Mechanical Detection Thresholds (MDT) using von Frey filaments. A positive threshold ratio [$(MDT_{affected}-MDT_{unaffected})/MDT_{affected}$] indicates increased tactile detection threshold (hypoesthesia) on the affected side. We further measured Mechanical Pain Thresholds (MPT) using pinprick stimulators. A positive threshold ratio [$(MPT_{unaffected}-MPT_{affected})/MPT_{unaffected}$] indicates decreased pain threshold (hyperalgesia) on the affected side. A procedure to measure allodynia was adapted from the dynamic mechanical allodynia test [93], in which a cotton ball, a Q-tip, and a brush were applied to the skin five times each, in a random order. An arithmetic mean of participants' ratings for each sensation from 0 (no sharp, pricking, stinging, or burning sensation) to 100 (most intense pain sensation imaginable) was used to quantify the severity of allodynia on the affected limb. We also measured Two-Point Discrimination thresholds (TPD) using a disk with one and two plastic tips separated by 2-15mm distance, which were applied to participants' index fingertips. Participants reported

whether they perceived touch on one point or two points on their finger. Starting from 7mm distance, we increased or decreased (down to a single tip) the distance according to a staircase procedure (analogous to that used for MDT and MPT), until we obtained five subthreshold (perceived touch on one point) and five suprathreshold (perceived touch on two points) values. A geometric mean of these 10 values was taken as a TPD threshold for each hand. A positive threshold ratio [$(TPD_{affected}-TPD_{unaffected})/TPD_{affected}$] indicates higher tactile discrimination threshold, that is, less precise discrimination ability of the affected hand.

In addition to contributing to the CRPS severity score, the following measures were used as secondary outcomes of autonomic and motor function of the affected relative to unaffected limb: temperature difference (affected–unaffected; a negative score indicates that the affected limb was colder; absolute values were also analysed); oedema (affected–unaffected; higher scores indicate greater swelling of the affected limb); grip strength (affected/unaffected; scores <1 indicate weaker strength of the affected hand); and ΔFTP distance (affected/unaffected; scores <1 indicate lower range of movement of the affected hand).

2.4.3.3. Tests of neuropsychological functions

In RS1-RS4, the participants completed six experimental tests of the following neuropsychological functions: visuospatial attention (Temporal Order Judgement, Landmark, and Greyscales tasks); mental representation of space (Mental Number Line Bisection task, MNLB); spatially-defined motor function; and body representation (Hand Laterality Recognition task). Detailed descriptions of the experimental materials and methods can be found in the trial protocol [33] (see Chapter 3). Below we summarise the key details of the administered tasks that are necessary to interpret the results.

All experimental tasks were programmed and administered using PsychoPy software [82]. For the tasks involving presentation of visual stimuli on a computer screen, a touchscreen (34.5cm x 19.4cm size, 1920 x 1080 pixels resolution) was positioned at 50cm viewing distance. In all tasks (except the MNLB), participant's head was stabilised by a chinrest and they were instructed to focus their gaze on a fixation cross that was aligned with their body midline. When a manual response was required, participant used their unaffected hand to press the buttons, which were aligned orthogonally to the required response format (i.e. for left/right responses, participant pressed colour-coded bottom/top buttons). A short practice session was completed before each task to familiarise the participant with the procedures and ensure that they could follow the instructions. Data for stimuli/responses in the left and right sides of space for all tasks were recoded after collection in terms of affected and unaffected space relative to each participant's CRPS-affected side.

2.4.3.3.1. Visuospatial attention

2.4.3.3.1.1. Temporal Order Judgement task

The Temporal Order Judgement (TOJ) measures covert spatial attention. On each trial, participant saw a pair of brief (10ms), identical, red light flashes, presented with different offsets onto a white table surface, one on each side of space (approximately 18° to the left and 18° to the right of a fixation point, located approximately 28cm away from their torso). Participant reported which of the two lights they perceived first (in one response block) or second (in another response block) by saying "left" or "right". The stimulus locations and responses were expressed relative to each participant's CRPS-affected side (i.e. as affected and unaffected). There were 10 temporal offsets between the lights (±10, ±30, ±60, ±120 and ±240ms; negative values indicate that the light on the affected side appeared first). Each temporal offset was presented 15 times in pseudorandom order, resulting in 150 trials per response block. The participant's responses to different temporal offsets were fitted with a cumulative Gaussian using a criterion of maximum likelihood to derive the Point of Subjective Simultaneity (PSS) for each block of the task. The PSSs from two response blocks were then averaged to account for any response bias [22]. The PSS expresses by how many milliseconds the light in the affected side of space had to precede (negative PSS) or follow (positive PSS) the light in the unaffected side of space for both lights to be perceived as simultaneous. Information that receives greater attention is perceived earlier than information that receives lesser attention [102]. Thus, a negative PSS value indicates reduced attention to the affected side of near space relative to the unaffected side.

2.4.3.3.1.2. Landmark task

The Landmark task [58] measures visual representation of relative horizontal distance in near space. On each trial, participants saw a fixation cross on constant display in the centre of the computer screen. After 500ms, a pair of landmarks (white 1.1° diameter circles) was presented simultaneously, one landmark to the left and one landmark to the right of the fixation cross. The landmarks were displayed for 300ms and were followed by a 200ms mask. While the distance between both landmarks was 15° across all trials, their relative distance from the fixation cross varied from ±8.1° to ±6.9° away from fixation in the horizontal plane by 0.1° increments (negative values represent the location of the left landmark, and positive values represent the location of the right landmark, relative to central fixation at 0°). Participants pressed a button to indicate whether the left or the right landmark appeared closer to (in one response block) or further from (in another response block) the fixation cross, which initiated the next trial. The stimulus locations and responses were expressed relative to each participant's CRPS-affected side (i.e. as affected and unaffected). Each of the 13 pairs of landmarks (six pairs in which the landmark on the affected side was further from fixation, six pairs in which the landmark on the unaffected side was further from fixation, and one pair in which both landmarks were equidistant) was presented 15 times in pseudorandom order, resulting in 195 trials per block. The participant's responses to different

relative landmark locations were fitted with a cumulative Gaussian using a criterion of maximum likelihood to derive the Point of Subjective Equality (PSE) for each block of the task. The PSEs from two response blocks were averaged to account for any potential response bias. The PSE expresses the relative distance (°) at which the landmark on the affected side of space had to be further from (negative PSE) or closer to (positive PSE) the fixation cross in order to perceive the two landmarks to be equidistant. A negative PSE value indicates underestimation of the distance on the affected relative to the unaffected side, and thus underrepresentation of the affected side of near space.

2.4.3.3.1.3. Greyscales task

The Greyscales task [80] measures overt spatial attention. On each trial, participants saw a pair of horizontal bars (9.95° or 12° x 1.95°) presented in the centre of a computer screen on constant display, one above the other. The two bars were filled with greyscales (i.e. a gradient of shading with one horizontal end darker than the other) and were mirror images of each other so that one bar was darker on the left side and the other bar was darker on the right side (expressed relative to each participant's CRPS-affected side, i.e. as affected and unaffected side). Participants pressed a button to indicate whether the top or the bottom bar appeared to be darker overall, which initiated a 150ms mask followed by the next trail. There were 40 trials in which the bars were presented in different vertical alignments. We calculated an index of spatial bias by subtracting the number of "unaffected" responses (choosing a bar darker on the unaffected side, regardless of its vertical alignment) from the number of "affected" responses, and dividing the difference by the total number of trials. A negative value indicates that a higher proportion of overall darkness judgements was made based on the unaffected sides of the stimuli, consistent with reduced attention to the affected relative to unaffected side.

2.4.3.3.2. Mental representation of space

The Mental Number Line Bisection (MNLB) task [104] measures mental representation of space, based on an implicit representation of numbers in a left-to-right linear arrangement [16]. On each trial, the experimenter read aloud a pair of numbers (from 2-98 number range) that were separated by an interval of 9, 16, 25, 36, 49, or 64 digits. Participants were instructed to verbally report the subjective midpoint between the given pair of numbers, without making any calculations. Each pair of numbers was presented once in ascending and once in descending order to account for any response bias, and each of the six intervals was repeated seven times, resulting in 84 trials presented in pseudorandom order. We calculated an index of spatial bias by subtracting participant's subjective midpoint from the objective midpoint number on each trial and averaging the scores across all trials. A negative index is consistent with overestimating the subjective midpoint towards larger numbers (i.e. a rightward bias). The results were expressed relative to each participant's CRPS-affected side, thus a negative index indicates a bias away from the

affected side of the mental representation of space, or underrepresentation of the affected side of mental space.

2.4.3.3.3. Spatially-defined motor function

The spatially-defined motor function task [60] measures directional hypokinesia and directional bradykinesia, that is slowing of initiation and execution of movements directed towards the affected relative to unaffected side. On each trial, participants focused on a fixation cross in the centre of a computer screen and held down a button with their index finger. After a 1500ms-3000ms interval, a black target (1.4° high "X") appeared 12° to the left or 12° to the right of fixation (i.e. in the left or right visual field, hereafter VF), in pseudorandom order, for 2000ms. Once the target appeared, participants were required to release the button, touch the screen, and return their index finger to the button as soon as possible, which initiated the next trial. There were 30 trials per block. We recorded the times elapsed between the target onset and button release (movement initiation time), and between the button release and touch on the computer screen (movement execution time). There were three hand starting positions, in which the button was aligned with the participant's body midline (central), located 25cm to the left from body midline (left), and located 25cm to the right from body midline (right). Hand starting positions and target locations (VFs) were expressed relative to each participant's CRPS-affected side, that is, as affected, central, and unaffected starting positions, and affected and unaffected VFs. Participants completed the task from each starting position twice, once with their unaffected hand, and once with their affected hand, resulting in six blocks in total. The order of the blocks was counterbalanced between participants, and they alternated between the affected and unaffected hand.

Participants' average movement initiation and execution times for each combination of hand starting position and VF were used to calculate indices of directional hypokinesia and bradykinesia towards the affected side [97], separately for each hand used to complete the task. Index A quantifies the speed of initiating movements towards the affected side (from central starting position) relative to the unaffected side (from affected starting position). This index was calculated as: [central starting position (affected VF – unaffected VF) – affected starting position (affected VF – unaffected VF)]. Index A allows to dissociate motor and perceptual neglect (i.e. effect of VF), however, it involves movement trajectories of different length. Thus, we also derived Index B that directly quantifies the speed of initiating movements of the same physical length towards the affected side (from central starting position) relative to the unaffected side (from affected starting position). Index B was calculated as: [central starting position (affected VF) – affected starting position (affected VF)]. Positive values of indices A and B indicate slowing of initiation of movements directed towards the affected relative to unaffected side, suggestive of directional hypokinesia towards the affected side. The same indices A and B were

calculated for movement execution times. Here, positive values suggest directional bradykinesia towards the affected side.

2.4.3.3.4. Body representation

The Hand Laterality Recognition task [99] measures body representation. On each trial, participants focused on a fixation cross in the centre of a computer screen. After 1000ms, an image of a hand (12.9° x 12.9°) appeared for 180ms, 8° to the left or 8° to the right of fixation (i.e. in the left or right VF). Participants were required to indicate as fast and as accurately as possible whether the image depicted a left or a right hand by pressing a button, which initiated the next trial. We measured accuracy and reaction times. There were 25 images of left hands in different postures and rotations from upright (0°, 90°, 180°, or 270°). The same images were mirror-reversed to create images of right hands in the same postures and rotations. Each image was presented once in the left and one in the right VF in pseudorandom order, resulting in 100 trials. The depicted hand was expressed relative to individual participant's CRPS-affected side, that is, as affected and unaffected hand.

Participants' accuracy rates and average reaction times to correctly responded-to trials for each task condition were averaged across two VFs, because the visual field effects were not the primary interest of this trial and will be reported elsewhere. We calculated the differences in accuracy rates and reaction times between depicted hands to obtain two indices of hand laterality recognition: accuracy index (unaffected hand – affected hand) and RT index (affected hand – unaffected hand). Positive values of each index indicate less accurate and slower recognition of depicted hands corresponding to participant's affected hand, relative to depicted hands corresponding to their unaffected hand. Thus, positive accuracy and RT indices suggest distorted representation of the CRPS-affected limb.

2.5. Statistical analyses

2.5.1. Sample size calculation

The study was powered to evaluate the effects of PA treatment on a change in the primary outcome of pain intensity between RS2 and RS3. We estimated [18] that a sample of 21 participants with CRPS per treatment group would provide 90% power to detect a minimal clinically significant reduction of 2 on the primary outcome of pain intensity (0-10 NRS; [20]), with a SD of 1.98 (based on our previous research [12]), and a 2-tailed alpha of 0.05.

2.5.2. Incomplete outcome data

Our primary analysis involved the intention-to-treat (ITT) population, that is, participants who received their allocated intervention, regardless of their treatment adherence or completion of the outcome assessments. Note that three participants who were allocated to PA treatment did not attend RS2 (n = 2) or did not meet the eligibility criteria in RS2 (n = 1), thus they were not trained

and did not receive any treatment (Figure 2), and were not included in the ITT sample. Therefore, the total ITT sample consisted of 49 participants. Eight participants dropped out of the study after having been trained in their allocated intervention (PA treatment n = 2, sham treatment n = 6), and four more participants were lost to long-term follow-up (n = 2 in each treatment group). These participants were retained in the ITT sample. To account for any missing data in the primary ITT analysis, we carried forward the baseline post-randomisation observation (RS2; the PGIC questionnaire data was only collected post-treatment, thus RS3 observation was carried forward). We report a supportive per-protocol analysis of those participants who completed their allocated treatment (missed no more than six treatment sessions) and provided complete outcome data in Text S6, Supplemental Material. The total number of participants with complete data was 41 (out of 42 as per sample calculation), because one participant in sham treatment group withdrew after we terminated the recruitment, therefore, we did not recruit any additional participant in their place. We chose ITT as primary analysis to address any potential selection bias associated with non-random loss of participants, and per-protocol as means of sensitivity analysis to assess the robustness of the ITT findings [71,112]. The results of the per-protocol analysis were broadly consistent with the ITT analysis.

Any missing questionnaire items were estimated using the individual participant's mean for the relevant subscale (0.08% of items across all sessions and participants). Any missing data from the self-report questionnaires, clinical assessments, and computer-based tasks within each research session were replaced by a mean score of the relevant treatment group on the same measure (0.08% of data points across all measures and sessions). Note that six participants completed the test of spatially-defined motor function only with their unaffected hand (due to exacerbation of pain, limited range of movement, or weakness of the affected hand), but their affected hand data was not replaced because data for each hand was analysed separately.

2.5.3. Analyses

We used IBM SPSS Statistics 25 [40], R 3.5.3 [86], and MATLAB 2018b [59] software to process and analyse the data. Data preparation procedures are reported in Text S3, Supplemental Material. Throughout, we reported bootstrapped bias-corrected and accelerated 95% confidence intervals (BCa 95% CIs) around all mean and median values. We used bootstrapped $\chi 2$ tests, bootstrapped t-tests (or their non-parametric alternatives in case of violation of parametric assumptions), and ANOVAs to compare mean values between treatment groups and between data collection time points. ANOVA is robust to moderate violations of normality and homogeneity of variance [6,7], and we used Greenhouse-Geisser corrections if the sphericity assumption was violated. However, where severe (i.e. more than borderline significant and in multiple conditions) violations of the assumptions of normality, homogeneity of variance, *and* sphericity were found, we used linear mixed models analyses with non-parametric bootstrapping procedures (n = 1000). For linear

mixed models analyses, a model term made a significant contribution to predicting an outcome when the 95% CI around the coefficient estimate (*B*) did not include zero. For the remaining analyses, statistical significance was defined as $p < .05$. We used one-tailed tests for comparisons for which we had directional hypotheses (i.e. RS2 vs. RS3 comparisons, as we predicted greater reductions on the outcome measures in PA than sham treatment group), and two-tailed tests for the remaining comparisons. We controlled for type I errors in the primary (but not exploratory) analyses by using Holm-Bonferroni correction for multiple comparisons within analysis of each outcome and reported adjusted *p* values (p_{adj}).

2.5.3.1. Descriptive characteristics and group matching

We performed a series of bootstrapped contrasts (t-tests or Mann-Whitney U tests for continuous variables, and $\chi 2$ tests for categorical variables) to determine whether the two treatment groups were successfully equated on the minimisation factors, as well as on the average POMS, LOTR, and PCOQ scores, and the extent of exposure (i.e. average number of logged treatment sessions).

2.5.3.2. Effects of PA treatment on the primary outcomes

To evaluate the effects of PA treatment on the first primary outcome of pain intensity and the time course of any changes, we conducted a 2 (Group: PA treatment, sham treatment) x 6 (Time: RS1, RS2, RS3, RS4, LTFU1, LTFU2) ANOVA. We planned sixteen a-priori contrasts to compare RS1 vs RS2, RS2 vs RS3, RS3 vs RS4, RS2 vs RS4, RS2 vs LTFU1, RS4 vs LTFU1, LTFU1 vs LTFU2, and RS2 vs LTFU2 within each treatment group.

To evaluate the effects of PA treatment on the second primary outcome of the CRPS severity score and the time course of any changes, we conducted a 2 (Group: PA treatment, sham treatment) x 4 (Time: RS1, RS2, RS3, RS4) ANOVA. We planned eight a-priori contrasts to compare RS1 vs RS2, RS2 vs RS3, RS3 vs RS4, and RS2 vs RS4 within each treatment group.

2.5.3.3. Effects of PA treatment on the secondary outcomes

To evaluate the effects of PA treatment on self-reported pain and psychological functioning, sensory, motor, and autonomic function, and neuropsychological functions, and the time course of any changes, we conducted 2x6 and 2x4 ANOVAs and planned the same contrasts as described for the analyses of the primary outcomes.

2.5.3.4. Predictors of the CRPS progression over time

To investigate whether any baseline factors could predict CRPS progression over time, independent of the treatment, we used the data from the total sample (N = 49) to perform exploratory best subsets regression analyses on the overall change in pain intensity and CRPS severity score throughout the course of the study. Change on these outcomes was quantified as individual regression slopes fitted to each participant's ratings of current pain intensity across RS1-LTFU2 and to each participant's CRPS severity scores across RS1-RS4. Negative slopes indicate greater improvement over time (i.e. reduction in pain and CRPS severity). Potential

explanatory variables included participants' demographic characteristics, self-reported pain and psychological functioning, sensory, motor, and autonomic function, and neuropsychological functions, as measured in RS1. We restricted the pool of potential predictors by excluding factors that lacked linear relationships with each outcome or were collinear with other predictors (see Text S4, Supplemental Material). Best subsets regression is an automated approach that performs an exhaustive search for the best subset of factors for predicting the outcome and returns the best model of each size (up to a specified number of predictors) [57]. Considering our sample size (N = 49), we compared best subsets models that included one up to five predictors of each outcome. From the five models, the one with the lowest Akaike Information Criterion (AIC) was preferred as best fit. To address a potential issue of overfitting, we also performed a five-fold cross-validation [49] of each of the five models suggested by best subsets regression analyses. This approach randomly splits the data set into five folds (subsets of observations). Each model is trained using the 80% of the data (four folds) and then tested on the remaining 20% of the data (one fold). This process is repeated until each fold has served as a test subset. The average of five recorded errors is a cross-validation (CV) error. The lowest CV error indicates best model performance.

3. Results

3.1. Participant characteristics

Table 1 presents baseline characteristics and comparisons between PA and sham treatment groups. On average, participants reported moderate pain intensity (6/10), comparable with previous studies on prism adaptation (5.8-6/10; [13,105]) and other neurocognitive treatments (5.3-7/10; [44,62,75]) for CRPS. Median CRPS severity score in our sample was higher than the average severity reported for individuals with stable CRPS in the validation study of this tool (13 vs. 11.2/16; [36]), possibly because we used stricter inclusion criteria (Budapest research diagnostic criteria; [34]). Our participants on average had longer CRPS duration compared to other studies of neurocognitive treatments for CRPS (58 vs. 5-24 months; [10,13,44,62,75,105]). The proportion of participants with CRPS affecting their right side of the body was consistent with a large population study [72], although it was lower than in small-sample studies on prism adaptation (41% vs. 71-80%; [13,105]). Both the mean age and proportion of females were consistent with those previously reported in CRPS [13,36,72,96,105]. The most common comorbidities in our participants were depression (37%), anxiety (22%), migraines (16%), fibromyalgia (14%), and asthma (14%). These conditions were found to be prevalent in CRPS in previous population studies [53,73]. The most common treatments in the current sample included weak or strong opioids (57%), anticonvulsants (47%), paracetamol (45%), antidepressants (45%), physio-, hydro-, or occupational therapy (39%), and nonsteroidal anti-inflammatory drugs (35%; see Table S1, Supplemental Material). Overall, demographic and clinical characteristics of our

sample appear to be representative of general population of people with CRPS [3,36,72,96] and comparable to those reported in previous research investigating neurocognitive treatments for CRPS [10,13,44,62,75,105], except for the longer average disease duration in our study.

The randomization procedure successfully equated the two treatment groups on the minimisation factors (Table 1). The two groups were also matched on baseline mean levels of optimism, mood disturbance, fear of movement, and expectations and criteria for success of the treatment (there were no significant differences between PA and sham treatment groups on any of the PCOQ items, $Us \geq 212.00$, $ps_{adj} \geq .27$, $ds \leq 0.51$).

Table 1 *Baseline (RS1) participant characteristics by treatment group (intention-to-treat analysis)*

Measure	Prism adaptation treatment (n = 23)	Sham treatment (n = 26)	Contrast
Minimisation factors			
Current pain intensity (/10) *M*	5.96 [5.02, 6.80]	6.15 [5.26, 7.00]	$t(47) = -0.33$, $p = .741$, $d = 0.10$
CRPS severity score (/16) *Mdn*	13.00 [12.07, 13.93]	12.50 [11.00, 13.00]	$U = 287.50$, $p = .809$, $d = 0.07$
Primarily affected arm (% right)	48%	35%	$\chi^2(1) = .88$, $p = .348$, $\phi = -0.13$
Pre-CRPS dominant hand (% right)	91%	92%	$\chi^2(1) = .16$, $p = .898$, $\phi = 0.02$
Sex (% female)	83%	85%	$\chi^2(1) = .04$, $p = .850$, $\phi = -0.03$
Age (years) *M*	47.35 [43.20, 51.95]	45.31 [39.85, 50.85]	$t(47) = 0.53$, $p = .601$, $d = -0.15$
CRPS in other body parts (% present)	13%	8%	$\chi^2(1) = .38$, $p = .537$, $\phi = -0.09$
Other non-CRPS pain (% present)	44%	39%	$\chi^2(1) = .13$, $p = .721$, $\phi = -0.05$
CRPS duration (months since diagnosis) *M*	61.26 [47.15, 75.12]	52.31 [39.49, 66.35]	$t(47) = 0.84$, $p = .388$, $d = -0.24$
Other control measures			
Optimism (LOTR; /24) *M*	13.00 [10.97, 15.07]	12.31 [11.00, 13.61]	$t(47) = 0.59$, $p = .560$, $d = -0.17$
Mood disturbance (POMS; /229) *M*	94.81 [79.96, 109.93]	84.22 [70.94, 98.08]	$t(47) = 0.97$, $p = .349$, $d = -0.28$
Fear of movement (TSK; /68) *M*	38.79 [35.45, 41.95]	40.38 [37.17, 43.35]	$t(47) = -0.65$, $p = .502$, $d = 0.19$
Number of logged treatment sessions (/29) *Mdn*	29.00 [28.54, 29.46]	29.00 [28.55, 29.45]	$U = 297.00$, $p = .977$, $d = 0.01$

LOTR, Revised Life Orientation Test; POMS, Profile of Mood States; TSK, Tampa Scale for Kinesiophobia. Bootstrapped bias-corrected and accelerated 95% confidence intervals are reported in square brackets, [BCa 95% CI]. There were no significant differences between groups on any measures.

Eight participants (16%) withdrew from the study after receiving their allocated treatment. They were excluded from per-protocol analysis (Text S6, Supplemental Material), but their RS2 data was carried forward for the purpose of the primary ITT analysis. We compared their baseline (RS1) pain intensity and CRPS severity against confidence intervals around the mean pain intensity and CRPS severity score of participants who remained in the trial. Out of those who dropped out, five participants had greater pain intensity and four participants had greater CRPS severity compared to those who remained. However, the same or lower pain intensity and CRPS severity scores were found in another three and four participants who dropped out, respectively.

3.2. Treatment adherence and participant blinding

Twenty-one out of 23 participants (91%) in the PA treatment group and 20 out of 26 participants (77%) in the sham treatment group missed no more than six treatment sessions according to their logbooks (see Table S1, Supplemental Material). Two participants in the PA and six participants in the sham treatment group missed more than six treatment sessions and/or did not provide post-treatment outcome data. The extent of exposure to treatment (i.e. average number of logged treatment sessions) was not significantly different between the two treatment groups (Table 1). The median recorded durations of the treatment sessions according to the participants' logbook entries were 2min 25s in the PA group and 2min in the sham treatment group.

At the end of RS4, we asked each participant (N = 41) which treatment they thought they received. They could respond "real [PA]", "sham", or "no idea". Similar proportions of participants in each group made correct (real: 12.2%; sham: 12.2%) or wrong (real: 12.2%; sham: 7.3%) guesses as to their actual treatment allocation, or responded that they had no idea (real: 26.8%; sham: 29.3%), $\chi^2(2) = .52$, $p = .771$, *Cramer's V* = 0.11. Only 12% of participants in each group correctly guessed their treatment allocation, therefore participant blinding was successful.

3.3. Effects of PA treatment on the primary outcomes

Despite the PA group showing some reduction in the current pain intensity scores immediately after treatment (RS3; Figure 4a), the ANOVA did not reveal any significant main effects of Time, $F(4.04, 189.81) = 1.82$, $p = 0.126$, $\eta^2_p = 0.04$, or Group, $F(1, 47) = 0.26$, $p = 0.615$, $\eta^2_p = 0.01$, nor did it show any significant interaction between these factors $F(4.04, 189.81) = 0.66$, $p = 0.624$, $\eta^2_p = 0.01$. This indicates that there were no significant changes in pain intensity over time in either treatment group. Thus, contrary to our hypothesis, PA treatment did not reduce pain intensity more than sham treatment.

Analysis of the CRPS severity scores (Figure 4b) showed a large significant main effect of Time, $F(2.28, 107.08) = 17.57$, $p < .001$, $\eta^2_p = 0.27$, indicating that regardless of treatment, CRPS severity decreased over time (Figure 4b). Contrasts revealed a significant reduction in CRPS severity immediately after treatment (RS3; *Mdn* = 11.00, BCa 95% CI [11.00, 11.00]) compared

to immediately before treatment (RS2; *Mdn* = 12.00, BCa 95% CI [12.00, 12.00]), Z = -3.91, p_{adj} = .002, d = 0.86. This reduction relative to RS2 was maintained four weeks after completing the treatment (RS4; *Mdn* = 11.00, BCa 95% CI [11.00, 11.00]), Z = -3.70, p_{adj} = .002, d = 0.81, but without further significant change from RS3, Z = -0.81, p_{adj} = .433, d = 0.16. CRPS severity did not change significantly between the first (RS1; *Mdn* = 13.00, BCa 95% CI [13.00, 13.00]) and the second baseline session, Z = -1.71, p_{adj} = .170, d = 0.35. There was no significant interaction effect, $F(2.28, 107.08) = 0.17$, p = .886, η^2_p < 0.01, nor was there any significant effect of Group, $F(1, 47) = 0.17$, p = .685, η^2_p < 0.01, on the CRPS severity scores. Thus, contrary to our hypothesis, CRPS severity did not decrease more following PA compared to sham treatment, but both groups improved over the treatment period.

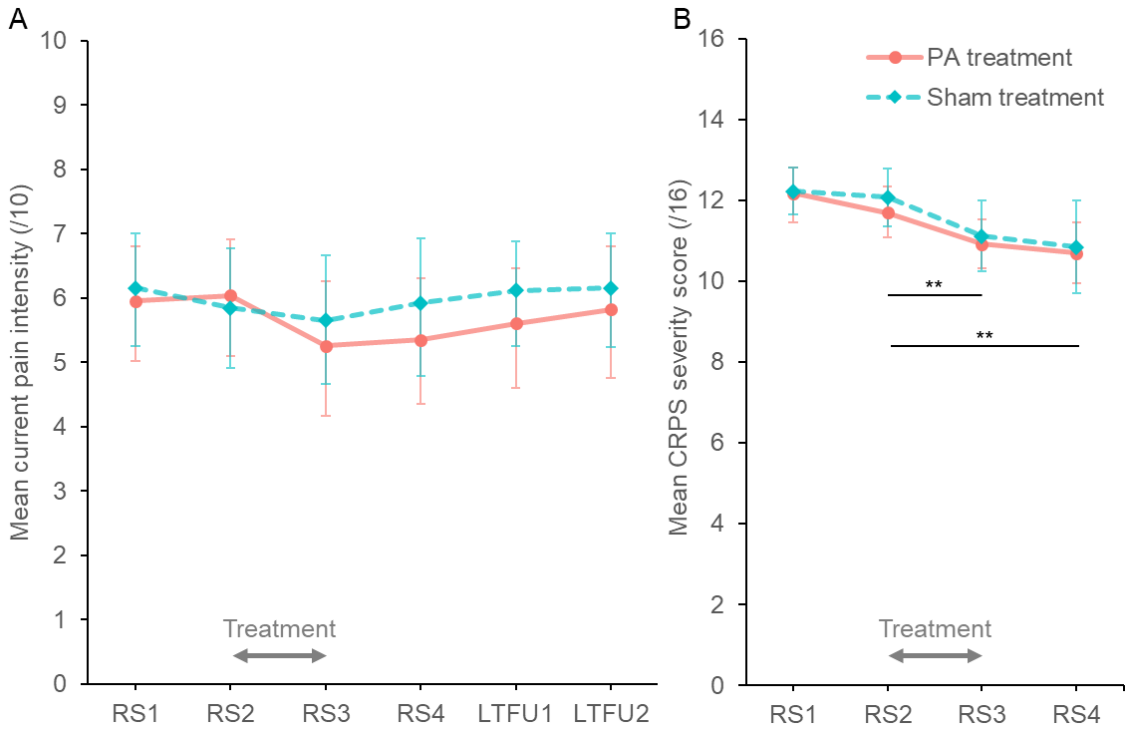

Figure 4. Primary outcomes (intention-to-treat analysis). Mean [BCa 95% CI] current pain intensity (A) and CRPS severity scores (B) in prism adaptation (PA; orange circles) and sham treatment (blue diamonds) groups in each time point. RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4; LTFU1 and LTFU2, long-term follow-up 1 and 2. Grey arrows indicate the treatment period. **Significant decrease in CRPS severity between RS2 and RS3, maintained at RS4, regardless of treatment, ps_{adj} < .01.

We compared mean changes in pain intensity and CRPS severity over the treatment period (RS3 – RS2) between PA and sham treatment groups. Effect sizes of these differences might be important for planning future studies. For current pain intensity, the effect size was small, d = 0.37, 95% CI [-0.20, 0.94]. Mean pain reduction in the PA treatment group was -0.78 points on 0-10 NRS scale, BCa 95% CI [-1.55, -0.15]. In the sham treatment group, mean pain reduction was -0.19 points, BCa 95% CI [-0.68, 0.28]. For CRPS severity score, the effect size was negligible, d = -0.13, 95% CI [-0.69, 0.43]. Mean CRPS severity reduction in the PA treatment

group was -0.78 points on 0-16 scale, BCa 95% CI [-1.19, -0.38]. In the sham treatment group, the mean CRPS severity reduction was -0.96 points, BCa 95% CI [-1.54, -0.38]. Individual pain and CRPS severity reduction scores over the treatment period are illustrated in Figure S1, Supplemental Material. On an individual level, five participants in the PA group and four in the sham group achieved clinically significant reductions in pain (i.e. at least two-point decrease on 0-10 NRS scale [20]). None of the participants achieved clinically significant reduction in CRPS severity (i.e. at least 4.9 points decrease on 0-16 scale, although this threshold is quite conservative) [36].

3.4. Effects of PA treatment on the secondary outcomes

3.4.1. Self-reported pain, body representation, and emotional functioning

A series of 2x6 ANOVAs was conducted on the self-report questionnaire scores to test the effects of PA on pain-related outcomes, body representation, and emotional functioning (see Table 2 for group average values across six time points; see Table 3 for ANOVA results).

Table 2 *Mean or median values [BCa 95% CI] of self-reported secondary outcome measures at each time point (intention-to-treat analysis)*

Measure	Treatment group	Time point					
		RS1	**RS2**	**RS3**	**RS4**	**LTFU1**	**LTFU2**
Pain							
Pain severity (BPI; /10) *M*	PA	5.91 [5.17, 6.58]	6.02 [5.28, 6.71]	5.41 [4.50, 6.26]	5.43 [4.55, 6.24]	5.62 [4.69, 6.48]	5.59 [4.69, 6.41]
	Sham	5.81 [5.02, 6.50]	5.95 [5.12, 6.78]	5.85 [5.04, 6.65]	5.84 [4.82, 6.74]	6.04 [5.12, 6.80]	5.95 [5.07, 6.73]
Pain interference (BPI; /10) *Mdn*	PA	6.71 [6.29, 6.71]	6.43 [5.00, 7.08]	5.29 [3.57, 6.43]	5.57 [4.71, 6.29]	6.00 [5.22, 6.14]	5.86 [4.57, 6.86]
	Sham	5.79 [5.00, 7.14]	5.86 [5.72, 5.86]	5.57 [5.43, 5.57]	5.64 [4.00, 6.14]	5.50 [3.71, 6.57]	5.72 [4.14, 6.57]
Neuropathic features of pain (PDQ; /38) *Mdn*	PA	26.00 [26.00, 26.00]	25.00 [20.00, 26.00]	24.00 [21.00, 27.00]	24.00 [20.00, 26.00]	26.00 [25.00, 26.00]	26.00 [21.46, 28.00]
	Sham	23.50 [21.50, 27.00]	24.00 [23.00, 24.00]	23.50 [20.00, 26.00]	22.50 [17.06, 26.00]	23.00 [20.00, 25.00]	22.50 [18.00, 26.00]
Body representation							
Body perception disturbance (BPDS; /57) *M*	PA	27.65 [22.83, 32.34]	27.78 [24.00, 31.22]	22.13 [17.88, 26.44]	24.39 [20.48, 28.57]	25.52 [21.78, 29.30]	24.57 [20.91, 28.44]
	Sham	28.96 [23.96, 33.76]	27.73 [21.98, 33.92]	29.00 [23.00, 35.36]	26.81 [20.92, 33.61]	26.77 [21.48, 32.68]	27.65 [22.53, 33.28]
Emotional functioning							
Fear of movement (TSK; /68) *M*	PA	38.79 [35.45, 41.95]	38.52 [35.02, 41.73]	37.43 [34.26, 40.50]	37.91 [34.70, 41.17]	38.74 [35.33, 41.95]	40.05 [36.22, 43.71]
	Sham	40.38 [37.17, 43.35]	39.73 [36.43, 42.81]	38.27 [34.90, 41.45]	37.42 [34.00, 40.71]	38.24 [34.97, 41.56]	37.27 [33.45, 40.79]
Mood disturbance (POMS; /229) *M*	PA	94.81 [79.96, 109.93]	98.25 [82.66, 113.93]	86.52 [71.16, 100.10]	86.21 [73.85, 99.00]	88.80 [74.42, 103.51]	95.54 [73.56, 117.95]
	Sham	84.22 [70.94, 98.08]	91.27 [76.05, 106.01]	83.21 [68.95, 96.96]	83.35 [68.76, 97.56]	82.42 [68.05, 96.53]	89.13 [70.81, 106.31]
Perceived improvement due to treatment							
Patient's global impression of change (PGIC; /7) *Mdn*	PA	-	-	2.00 [2.00, 4.00]	3.00 [3.00, 3.00]	2.00 [2.00, 4.00]	3.00 [2.00, 3.00]
	Sham	-	-	3.00 [1.00, 4.00]	4.00 [3.00, 4.00]	2.00 [2.00, 3.00]	2.00 [1.00, 4.00]

BPI, Brief Pain Inventory; PDQ, Pain Detect Questionnaire; BPDS, Bath CRPS Body Perception Disturbance Scale; TSK, Tampa Scale for Kinesiophobia; POMS, Profile of Mood States; PA, prism adaptation treatment; Sham, sham treatment; RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4; LTFU1 and LFTU2, long-term follow-ups 1 and 2.

Table 3 *Analysis of variance results for secondary outcome measures (intention-to-treat analysis)*

Measure	**Effect**	***df*†**	***F***	***p***	η^2_p
Self-report questionnaires					
Pain severity (BPI)	Time	4.12, 193.81	1.24	0.295	0.03
	Group	1, 47	0.19	0.664	< 0.01
	Time x Group	4.12, 193.81	1.06	0.379	0.02
Pain interference (BPI)	Time*	2.88, 135.32	2.84	0.043	0.06
	Group	1, 47	0.04	0.838	< 0.01
	Time x Group	2.88, 135.32	0.74	0.526	0.02
Neuropathic features of pain (PDQ)	Time*	3.29, 154.50	3.32	0.018	0.07
	Group	1, 47	0.32	0.574	0.01
	Time x Group	3.29, 154.50	0.61	0.625	0.01
Body perception disturbance (BPDS)	Time	3.41, 160.11	2.43	0.059	0.05
	Group	1, 47	0.57	0.455	0.01
	Time x Group*	3.41, 160.11	2.60	0.047	0.05
Fear of movement (TSK)	Time	3.86, 181.61	2.41	0.053	0.05
	Group	1, 47	< 0.01	0.993	< 0.01
	Time x Group*	3.86, 181.61	2.89	0.025	0.06
Mood disturbance (POMS)	Time	3.60, 169.21	2.29	0.069	0.05
	Group	1, 47	0.36	0.554	0.01
	Time x Group	3.60, 169.21	0.25	0.894	0.01
Patient's global impression of change (PGIC)	Time	3, 120	0.96	0.414	0.02
	Group	1, 40	0.02	0.890	< 0.01
	Time x Group	3, 120	0.56	0.644	0.01
Clinical assessments					
Allodynia (affected limb)	Time	2.23, 104.67	1.03	0.367	0.02
	Group	1, 47	0.25	0.616	0.01
	Time x Group	2.23, 104.67	0.35	0.730	0.01
Absolut temperature difference	Time	3, 141	0.43	0.731	0.01
	Group	1, 47	0.16	0.695	< 0.01
	Time x Group	3, 141	0.63	0.595	0.01
Oedema difference	Time	2.41, 113.08	0.99	0.387	0.02
	Group	1, 47	0.06	0.805	< 0.01
	Time x Group	2.41, 113.08	1.86	0.153	0.04

Measure	Effect	*df*†	*F*	*p*	η^2_p
Experimental tests of neuropsychological functions					
Temporal Order Judgement task (PSS)	Time	1.70, 79.69	1.08	0.335	0.02
	Group	1, 47	0.16	0.692	< 0.01
	Time x Group	1.70, 79.69	0.63	0.512	0.01
Greyscales task	Time	2.17, 101.82	0.57	0.581	0.01
	Group	1, 47	0.02	0.899	< 0.01
	Time x Group	2.17, 101.82	0.52	0.609	0.01
Mental Number Line Bisection task	Time	2.39, 112.17	0.48	0.656	0.01
	Group	1, 47	0.50	0.481	0.01
	Time x Group	2.39, 112.17	0.14	0.899	< 0.01
Hand laterality recognition Accuracy Index	Time	3, 141	2.39	0.072	0.05
	Group	1, 47	1.54	0.221	0.03
	Time x Group	3, 141	0.44	0.723	0.01
Hand laterality recognition Reaction Time Index	Time	3, 141	1.32	0.269	0.03
	Group	1, 47	0.05	0.826	< 0.01
	Time x Group	3, 141	1.48	0.224	0.03

* Statistically significant effect ($p < .05$).

† Greenhouse-Geisser adjusted degrees of freedom are reported where sphericity assumption was violated. BPI, Brief Pain Inventory; PDQ, Pain Detect Questionnaire; BPDS, Bath CRPS Body Perception Disturbance Scale; TSK, Tampa Scale for Kinesiophobia; POMS, Profile of Mood States. PSS, Point of Subjective Simultaneity.

A significant main effect of Time on pain interference (BPI) indicated that participants reported less interference from RS2 (*Mdn* = 6.00, BCa 95% CI [5.57, 6.71]) to RS4 (*Mdn* = 5.57, BCa 95% CI [4.86, 5.86]), regardless of treatment, $Z = -2.56$, $p_{adj} = .040$, $d = 0.54$. There were no significant changes in pain interference between other time points, $Zs \leq 1.86$, $ps_{adj} \geq .273$, $ds \leq 0.38$. A significant main effect of Time for neuropathic features of pain (PDQ) suggested that participants' scores decreased over time, regardless of treatment group. However, follow-up analyses revealed no significant differences between any of the time points of interest $Zs \leq 1.76$, $ps_{adj} \geq .576$, $ds \leq 0.36$. An ANOVA on body perception disturbance (BPDS) revealed a significant interaction between Time and Group. While there were no changes in the sham treatment group, PA group showed reductions in body perception disturbance over time, yet these effects did not withstand correction for multiple comparisons, $ts \leq 2.86$, $ps_{adj} \geq .336$, $ds \leq 0.54$. An ANOVA on fear of movement also revealed a significant interaction between Time and Group. While there were no changes in the PA group, the sham treatment group showed reductions in fear of movement over time; however, these effects did not withstand correction for multiple comparisons, $ts \leq 2.63$, ps_{adj}

≥ .312, *ds* ≤ 0.26. There were no other significant main effects or interactions (see Table 3). Participants' global impression of change due to treatment (PGIC) also did not differ between PA and sham treatment group at any of the post-treatment time points and indicated that on average participants in both groups perceived their symptoms to be either "almost the same", or "a little better" (2-3 out of 7). Overall, contrary to our hypothesis, we found no evidence of significantly greater reductions in self-reported pain-related and psychological disturbances following PA compared to sham treatment.

Average daily logbook ratings of pain intensity, symptom interference, and range of movement for each group are illustrated in Figure S2, Supplemental Material. The PA and sham treatment groups did not differ on any of these measures at any time point [pain intensity: *ts*(45) ≤ 1.75, *ps* ≥ .093, *ds* ≤ 0.51; symptom interference: *ts*(45) ≤ 1.24, *ps* ≥ .240, *ds* ≤ 0.36; range of movement: *ts*(45) ≤ 1.81, *ps* ≥ .062, *ds* ≤ 0.53]. The median number of days from the beginning of treatment to reach peak improvement and from peak improvement to return to baseline on each of these measures were similar in the PA and sham treatment groups (see Text S5, Supplemental Material).

3.4.2. Sensory, motor, and autonomic functions

A series of 2x4 ANOVAs was conducted on the scores from clinical assessments to test the effects of PA on sensory, autonomic, and motor functions. We reported group average values for these measures across four time points in Table 4. For the allodynia on the affected limb, absolute temperature difference, and oedema difference data, the ANOVA results are reported in Table 3. The MDT, MPT, and TPD threshold ratios data, as well as grip strength and ΔFTP ratios data were analysed using linear mixed models due to severe violations of the assumptions of normality, homogeneity of variance, and/or sphericity. The results of these analyses are reported in Table 5.

A significant main effect of Time on the MPT ratios indicated that participants experienced less hyperalgesia on the affected relative to unaffected limb over the treatment period, regardless of treatment. However, this effect did not withstand correction for multiple comparisons, and there were no significant differences between other time points, *Zs* ≤ 1.60, ps_{adj} ≥ .208, *d* ≤ 0.33. We also found a significant interaction between Time and Group on the MPT ratios. Despite the PA group showing a reduction in hyperalgesia over the treatment period, this effect did not withstand correction for multiple comparisons, and there were no other changes on MPT ratios in either group, *Zs* ≤ 1.68, ps_{adj} ≥ .440, *ds* ≤ 0.51.

Our analyses did not reveal any other significant main effects or interactions (see Tables 3 and 5). Overall, contrary to our hypothesis, we found no evidence of significantly greater improvements in sensory, autonomic, or motor functions following PA compared to sham treatment, except for the trend towards predicted reduction in hyperalgesia (MPT ratio) in the PA group over the treatment period.

Table 4 *Mean or median values [BCa 95% CI] of sensory, autonomic, and motor secondary outcome measures at each time point (intention-to-treat analysis)*

Measure	**Treatment group**	**Time point**			
		RS1	**RS2**	**RS3**	**RS4**
Sensory functions					
Mechanical Detection Threshold ratio [(affected – unaffected) / affected] *Mdn*	PA	-0.04 [-0.43, 0.38]	-0.35 [-1.12, 0.17]	-0.44 [-0.84, -0.06]	-0.54 [-1.51, -0.10]
	Sham	-0.30 [-1.37, 0.24]	-0.05 [-0.25, 0.17]	-0.14 [-0.91, 0.30]	-0.22 [-0.76, 0.28]
Mechanical Pain Threshold ratio [(unaffected – affected) / unaffected] *Mdn*	PA	0.62 [0.06, 0.69]	0.50 [0.43, 0.56]	0.07 [-0.32, 0.66]	0.50 [0.06, 0.69]
	Sham	0.57 [0.24, 0.67]	0.56 [0.38, 0.73]	0.50 [0.32, 0.71]	0.43 [0.24, 0.78]
Allodynia (affected; /100) *Mdn*	PA	14.00 [5.76, 26.67]	18.87 [4.67, 30.89]	16.90 [6.00, 26.17]	10.73 [2.87, 18.26]
	Sham	20.50 [9.00, 33.83]	14.37 [6.47, 25.03]	13.87 [6.47, 46.47]	18.03 [7.33, 33.33]
Two-Point Discrimination Threshold ratio [(affected – unaffected) / affected] *Mdn*	PA	-0.06 [-0.16, 0.11]	0.00 [-0.08, 0.13]	-0.08 [-0.20, 0.00]	-0.04 [-0.21, 0.03]
	Sham	0.15 [-0.07, 0.31]	-0.13 [-0.25, 0.10]	-0.09 [-0.17, 0.00]	0.05 [-0.30, 0.22]
Autonomic functions					
Absolute temperature difference (affected – unaffected; °C) *Mdn*	PA	0.47 [0.27, 1.40]	0.30 [0.14, 0.68]	0.35 [0.20, 0.73]	0.50 [0.17, 1.17]
	Sham	0.47 [0.30, 0.78]	0.82 [0.53, 1.07]	0.77 [0.43, 1.05]	0.67 [0.40, 1.00]
Oedema difference (affected – unaffected; cm) *M*	PA	-0.01 [-0.42, 0.43]	-0.04 [-0.36, 0.28]	-0.19 [-0.58, 0.21]	-0.23 [-0.64, 0.20]
	Sham	-0.11 [-0.51, 0.34]	-0.02 [-0.40, 0.38]	-0.12 [-0.52, 0.30]	0.04 [-0.33, 0.43]
Motor functions					
Grip strength ratio (affected / unaffected) *Mdn*	PA	0.35 [0.17, 0.39]	0.31 [0.25, 0.44]	0.35 [0.30, 0.46]	0.39 [0.30, 0.46]
	Sham	0.32 [0.20, 0.65]	0.33 [0.18, 0.58]	0.44 [0.26, 0.60]	0.42 [0.23, 0.60]
Finger-to-palm distance ratio (affected / unaffected) *Mdn*	PA	0.70 [0.60, 0.88]	0.67 [0.61, 0.87]	0.73 [0.63, 0.84]	0.79 [0.70, 0.82]
	Sham	0.69 [0.55, 0.90]	0.72 [0.53, 0.88]	0.79 [0.53, 0.89]	0.77 [0.60, 0.93]

PA, prism adaptation treatment; Sham, sham treatment; RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4.

Table 5 *The results of the bootstrapped linear mixed models regressions of scores for the tests of sensory and motor function, and a test of visuospatial attention (intention-to-treat analysis)*

Model term	**Coefficient estimate [95% CI]**					
	Sensory functions			**Motor functions**		**Visuospatial attention**
	Mechanical Detection Threshold ratio	**Mechanical Pain Threshold ratio**	**Two-Point Discrimination Threshold ratio**	**Grip ratio**	**Delta finger-to-palm ratio**	**Landmark task (PSE)**
Intercept	-1.26 [-2.22, -0.37]*	0.19 [-0.10, 0.46]	-0.02 [-0.14, 0.11]	0.38 [0.33, 0.44]*	0.60 [0.51, 0.70]*	0.07 [-0.05, 0.19]
Time (RS2 = 0)						
RS1	-0.44 [-2.03, 1.01]	-0.43 [-0.99, 0.07]	-0.02 [-0.20, 0.15]	-0.03 [-0.08, 0.01]	-0.04 [-0.12, 0.04]	0.08 [-0.18, 0.38]
RS3	-0.24 [-1.21, 0.65]	-0.49 [-0.99, -0.06]*	-0.14 [-0.32, 0.03]	0.01 [-0.05, 0.06]	-0.02 [-0.11, 0.05]	0.06 [-0.09, 0.21]
RS4	-0.56 [-1.69, 0.50]	-0.14 [-0.52, 0.24]	-0.04 [-0.21, 0.13]	0.03 [-0.03, 0.09]	0.03 [-0.04, 0.11]	-0.02 [-0.16, 0.14]
Group (PA = 0)						
Sham	0.93 [-0.64, 2.54]	0.06 [-0.35, 0.45]	-0.20 [-0.43, 0.03]	0.04 [-0.06, 0.12]	0.14 [-0.05, 0.30]	0.01 [-0.17, 0.20]
Time x Group (RS2, PA = 0)						
RS1, Sham	-0.01 [-1.63, 1.79]	0.34 [-0.33, 1.03]	0.27 [-0.08, 0.64]	0.01 [-0.05, 0.08]	0.03 [-0.07, 0.13]	0.04 [-0.29, 0.34]
RS3, Sham	-0.77 [-2.52, 0.95]	0.65 [0.08, 1.32]*	0.16 [-0.11, 0.44]	0.05 [-0.03, 0.12]	0.05 [-0.04, 0.16]	-0.05 [-0.24, 0.15]
RS4, Sham	0.45 [-1.08, 1.91]	0.16 [-0.41, 0.72]	-0.08 [-0.53, 0.30]	0.01 [-0.09, 0.09]	0.00 [-0.09, 0.10]	0.01 [-0.18, 0.21]

* Significant effect (95% CI around the coefficient estimate does not include 0).

The reference condition for dummy variable coding is indicated within parentheses for each term.

PA, prism adaptation treatment; Sham, sham treatment; RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4; PSE, Point of Subjective Equality.

3.4.3. Neuropsychological functions

A series of 2x4 ANOVAs was performed on the scores from experimental neuropsychological tasks to test the effects of PA on visuospatial attention, mental representation of space, spatially-defined motor function, and body representation. Table 6 includes group average scores for participants' performance on these measures across four time points. Negative scores on the tests of visuospatial attention and mental representation of space would indicate a bias away from the affected side. However, confidence intervals around the baseline scores on these tests include zero, suggesting that participants did not show significant spatial biases. Positive values of directional hypokinesia and bradykinesia indices would indicate slowing of movements directed towards the affected side. Yet participants' median indices were both positive and negative depending on the specific condition, suggesting that there were no systematic spatially-defined motor deficits at baseline. Positive accuracy and reaction time indices on the test of body representation would suggest less accurate and slower laterality recognition for the images of affected hands. However, participants' scores were mostly negative at baseline. Furthermore, most of the confidence intervals included zero, indicating that there were no differences in recognition of the affected relative to unaffected hands. The ANOVA results for the TOJ, Greyscales, MNLB, and Hand Laterality Recognition tasks are reported in Table 3. Due to severe violations of the assumptions of normality, homogeneity of variance, and/or sphericity, the data for the Landmark task and spatially-defined motor function were analysed using linear mixed models (see Tables 5 and 7, respectively).

There were no significant main effects or interactions on any of the measures of visuospatial attention, mental representation of space, or body representation. Linear mixed model analyses revealed a significant main effect of group on Index B of directional bradykinesia when using the unaffected hand. This effect indicates that participants in PA group (Mdn = 42.39, BCa 95% CI [20.42, 150.32]) showed greater directional bradykinesia on this index (i.e. they were slower to execute movements directed towards the affected relative to unaffected side) compared to participants in sham treatment group (Mdn = 12.07, BCa 95% CI [-26.41, 40.93]), regardless of time point of the study, U = 136.00, p = .022, d = 1.06. No significant effects or interactions were found on any other indices of spatially-defined motor function.

Overall, contrary to our hypothesis, there was no evidence of greater improvements in spatial cognition, motor control, or body representation following PA compared to sham treatment.

Table 6 *Mean or median values [BCa 95% CI] of neuropsychological secondary outcome measures at each time point (intention-to-treat analysis)*

Measure	Treatment group	Time point			
		RS1	RS2	RS3	RS4
Visuospatial attention					
Temporal Order Judgement task (PSS; ms) *Mdn*	PA	0.16 [-13.82, 9.02]	-3.26 [-14.51, 8.35]	-1.00 [-8.65, 9.71]	5.18 [-1.74, 10.87]
	Sham	-0.05 [-7.40, 7.06]	-0.75 [-8.55, 6.65]	1.17 [-6.16, 7.33]	-2.12 [-10.48, 6.07]
Landmark task (PSE; °) *Mdn*	PA	0.04 [-0.20, 0.28]	0.09 [-0.01, 0.19]	0.03 [-0.09, 0.40]	-0.02 [-0.13, 0.19]
	Sham	0.06 [-0.07, 0.21]	0.06 [-0.12, 0.17]	-0.05 [-0.09, 0.10]	0.05 [-0.04, 0.10]
Greyscales task *M*	PA	0.17 [-0.07, 0.41]	0.12 [-0.11, 0.34]	0.08 [-0.13, 0.30]	0.11 [-0.12, 0.34]
	Sham	0.09 [-0.08, 0.26]	0.12 [-0.08, 0.32]	0.07 [-0.10, 0.25]	0.14 [-0.06, 0.31]
Mental representation of space					
Mental Number Line Bisection task *M*	PA	-0.06 [-0.76, 0.67]	-0.10 [-0.73, 0.54]	0.04 [-0.58, 0.63]	-0.06 [-0.55, 0.42]
	Sham	0.12 [-0.51, 0.77]	0.24 [-0.50, 0.99]	0.39 [-0.36, 1.21]	0.31 [-0.34, 0.99]
Spatially-defined motor function					
Directional hypokinesia, affected hand, Index A (MIT; ms) *Mdn*	PA	-4.88 [-41.02, 29.55]	-2.23 [-40.87, 16.76]	-15.41 [-58.35, -9.44]	-21.93 [-40.85, -9.44]
	Sham	-15.65 [-79.21, 26.94]	21.51 [-21.38, 56.06]	-24.31 [-61.88, -12.51]	-12.26 [-47.44, 16.73]
Directional hypokinesia, affected hand, Index B (MIT; ms) *Mdn*	PA	-37.53 [-90.19, 16.61]	-25.46 [-84.04, 13.63]	-48.49 [-80.33, -22.88]	4.10 [-40.19, 10.67]
	Sham	-40.43 [-48.52, -21.96]	-0.40 [-61.60, 15.61]	-8.19 [-48.87, 13.72]	3.32 [-43.06, 20.37]
Directional hypokinesia, unaffected hand, Index A (MIT; ms) *Mdn*	PA	0.14 [-15.93, 19.88]	10.28 [1.15, 22.22]	-6.76 [-19.29, 13.43]	-2.78 [-45.45, 13.43]
	Sham	5.57 [-24.54, 26.03]	-7.88 [-20.59, 14.27]	6.88 [-15.63, 18.92]	2.51 [-13.48, 23.38]
Directional hypokinesia, unaffected hand, Index B (MIT; ms) *Mdn*	PA	4.84 [-6.43, 11.89]	9.41 [-17.73, 25.19]	-3.40 [-21.35, 33.52]	7.43 [-26.43, 38.21]
	Sham	-23.63 [-48.34, 12.93]	9.18 [-12.92, 28.54]	11.01 [-10.84, 28.46]	16.47 [-2.91, 26.35]
Directional bradykinesia, affected hand, Index A (MET; ms) *Mdn*	PA	97.95 [23.29, 216.69]	64.71 [22.36, 123.85]	46.11 [14.19, 72.77]	52.74 [22.18, 66.01]
	Sham	3.73 [-32.67, 67.35]	50.72 [-5.50, 64.21]	31.79 [3.63, 87.48]	41.09 [11.92, 64.21]
Directional bradykinesia, affected hand, Index B (MET; ms) *Mdn*	PA	-49.68 [-125.50, -8.16]	-180.86 [-235.79, -16.96]	-124.70 [-129.09, -122.32]	-78.67 [-115.85, -42.31]
	Sham	-63.53 [-149.00, -57.28]	-103.18 [-170.48, -54.09]	-77.46 [-97.96, -17.51]	-75.60 [-99.62, -48.41]

Measure	Treatment group	Time point			
		RS1	RS2	RS3	RS4
Directional bradykinesia, unaffected hand, Index A (MET; ms) *Mdn*	PA	48.80 [35.53, 64.67]	69.36 [35.74, 103.71]	79.01 [45.24, 99.85]	79.78 [59.27, 116.99]
	Sham	86.46 [54.45, 127.39]	69.84 [24.68, 113.96]	84.79 [76.26, 86.26]	48.80 [35.53, 64.67]
Directional bradykinesia, unaffected hand, Index B (MET; ms) *Mdn*	PA	31.39 [-13.35, 64.92]	69.35 [25.05, 98.88]	36.70 [21.07, 63.50]	20.37 [-13.72, 66.72]
	Sham	-28.35 [-71.98, 41.21]	3.34 [-39.16, 44.61]	28.60 [6.71, 53.45]	3.38 [-22.98, 12.57]
Body representation					
Hand laterality recognition Accuracy Index (%) *M*	PA	-1.65 [-5.66, 2.34]	-2.26 [-5.68, 1.43]	1.30 [-2.23, 4.37]	1.57 [-2.70, 6.00]
	Sham	2.77 [-1.32, 7.37]	-1.77 [-5.83, 2.21]	3.92 [0.19, 7.72]	2.54 [-2.00, 6.83]
Hand laterality recognition Reaction Time Index (ms) *M*	PA	-97.74 [-268.99, 70.43]	-57.20 [-187.91, 70.02]	-37.44 [-155.06, 78.98]	-130.05 [-240.98, -27.84]
	Sham	-236.04 [-448.24, -65.14]	-129.37 [-263.61, 21.19]	-28.65 [-173.14, 95.70]	19.77 [-112.95, 161.67]

PSS, Point of Subjective Simultaneity; PSE, Point of Subjective Equality; MIT, movement initiation time; MET, movement execution time; PA, prism adaptation treatment; Sham, sham treatment; RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4.

Table 7 *The results of the bootstrapped linear mixed models regressions of indices of directional hypokinesia and bradykinesia for the spatially-defined motor function task (intention-to-treat analysis)*

Model term	**Coefficient estimate [95% CI]**							
	Directional hypokinesia (MIT)				**Directional bradykinesia (MET)**			
	Affected hand		**Unaffected hand**		**Affected hand**		**Unaffected hand**	
	Index A	**Index B**	**Index A**	**Index B**	**Index A**	**Index B**	**Index A**	**Index B**
Intercept	-11.95 [-40.94, 19.61]	-23.14 [-52.63, 7.40]	8.63 [-6.39, 24.24]	0.94 [-21.21, 20.64]	6.56 [-61.92, 68.33]	-93.90 [-175.79, 3.94]	84.07 [62.32, 106.44]*	65.60 [34.96, 95.76]*
Time (RS2 = 0)								
RS1	8.39 [-31.73, 49.37]	-20.72 [-67.93, 25.85]	-4.96 [-35.64, 29.32]	2.44 [-25.43, 30.40]	101.53 [-0.10, 209.18]	41.98 [-57.89, 149.11]	15.05 [-21.41, 49.03]	-25.10 [-76.04, 24.74]
RS3	-31.21 [-83.79, 13.52]	-45.39 [-111.04, 7.52]	-9.90 [-38.46, 15.04]	0.68 [-25.73, 28.63]	7.81 [-79.00, 93.41]	-40.25 [-142.74, 53.50]	5.55 [-23.80, 37.85]	-22.18 [-59.45, 12.77]
RS4	-15.50 [-62.46, 33.97]	25.65 [-25.47, 75.22]	-24.33 [-52.94, 2.60]	-6.41 [-49.64, 34.72]	20.26 [-57.47, 110.05]	53.08 [-41.08, 155.80]	-6.30 [-34.26, 22.32]	-32.55 [-73.00, 7.92]
Group (PA = 0)								
Sham	34.27 [-22.36, 87.39]	20.52 [-24.27, 64.73]	-3.65 [-26.22, 21.47]	14.98 [-15.77, 50.03]	55.82 [-17.47, 135.08]	-57.61 [-197.35, 65.94]	-4.43 [-39.74, 29.20]	-67.00 [-109.25, -24.86]*
Time x Group (RS2, PA = 0)								
RS1, Sham	-45.16 [-125.14, 38.62]	18.55 [-61.15, 97.28]	2.02 [-43.86, 42.90]	-21.72 [-63.89, 21.18]	-110.69 [-233.29, 13.49]	-27.37 [-171.51, 103.83]	-7.62 [-59.42, 42.81]	13.68 [-57.81, 81.17]
RS3, Sham	-26.61 [-99.16, 46.45]	12.83 [-71.22, 102.89]	10.74 [-25.81, 45.99]	-0.99 [-41.65, 39.36]	0.85 [-111.67, 107.19]	70.90 [-70.74, 203.15]	-11.42 [-56.67, 30.87]	43.84 [-2.70, 93.38]
RS4, Sham	-29.67 [-115.20, 54.26]	-13.56 [-99.10, 70.45]	25.33 [-10.84, 61.39]	20.53 [-31.38, 77.00]	-11.91 [-106.35, 81.27]	-8.74 [-142.49, 124.83]	-19.00 [-61.68, 28.21]	26.31 [-24.08, 75.24]

* Significant effect (95% CI around the coefficient estimate does not include 0).

The reference condition for dummy variable coding is indicated within parentheses for each term.

PA, prism adaptation treatment; Sham, sham treatment; RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4; MIT, movement initiation time; MET, movement execution time.

3.5. Exploratory correlational and subgroup analyses

We explored the possibility that we did not observe any effects of PA treatment on pain or CRPS severity because participants did not show attention bias away from the affected side or body representation distortion (see Table 6 and [31], Chapter 4), which PA should have normalised, according to its hypothesised mechanisms. If baseline "neglect-like" bias and/or body representation disturbance are necessary for PA to have therapeutic effects, these should be observed for the subgroup of participants who did show reduced attention to their affected side and/or distorted body representation. However, exploratory correlational and subgroup analyses suggest that this was not the case in our study.

Correlational analyses are illustrated in Figures 5 and 6. We plotted individual pain intensity and CRPS severity reduction scores from immediately before treatment to immediately after treatment (RS3 – RS2), against individual RS2 scores on tests of visuospatial attention and mental representation of space (Figure 5), and body representation (Figure 6). Visual exploration of participant-level data and Pearson's correlation coefficients for each treatment group indicate that there were no apparent relationships between the changes on the primary outcomes of pain intensity or CRPS severity and any of the spatial biases or body representation distortion, except moderate significant correlation between change in CRPS severity and baseline bias on the Greyscales task in the PA group and Hand laterality recognition reaction time index in the Sham treatment group.

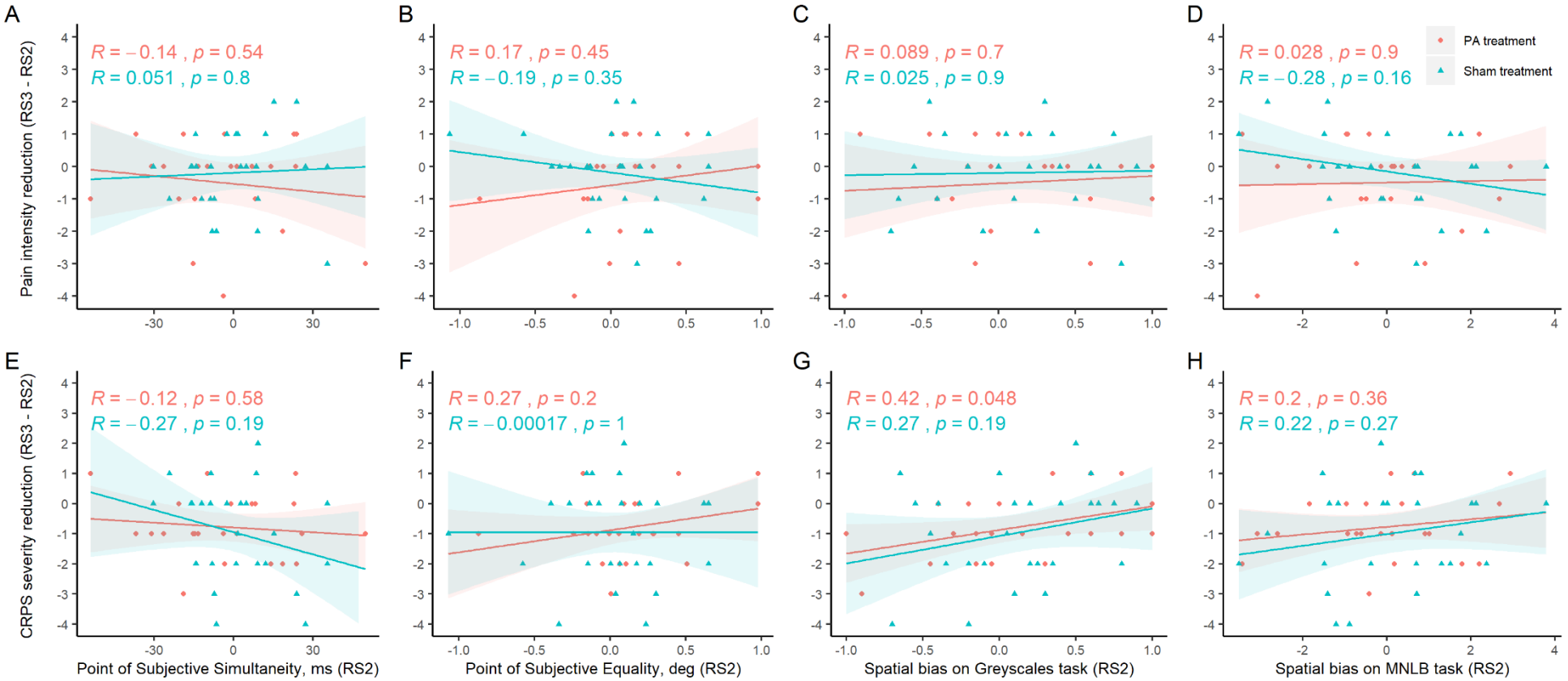

Figure 5. Scatterplots of changes on the primary outcomes vs. baseline performance on tests of spatial cognition (intention-to-treat analysis). Relationships between individual participants' change in pain intensity (top panel) and CRPS severity (bottom panel) over the treatment period (between RS2, research session 2, and RS3, research session 3) and their baseline (RS2) performance on the Temporal Order Judgement (A, E), Landmark (B, F), Greyscales (C, G), and Mental Number Line Bisection (MNLB; D, H) tasks are illustrated. Negative scores for pain and CRPS severity indicate reduction of these outcomes (i.e. improvement). Negative scores on the tests of spatial cognition indicate reduced attention to and/or representation of the affected relative to unaffected side. Lines of best fit with confidence intervals (shaded surfaces) are superimposed for each treatment group. Pearson's correlation coefficients (R) are reported for the relationships between change in pain (top panel) or CRPS severity (bottom panel) and performance on the tests of spatial cognition in PA (orange) and sham treatment (blue) groups. For pain reduction score, one observation was removed as an outlier (score = -7).

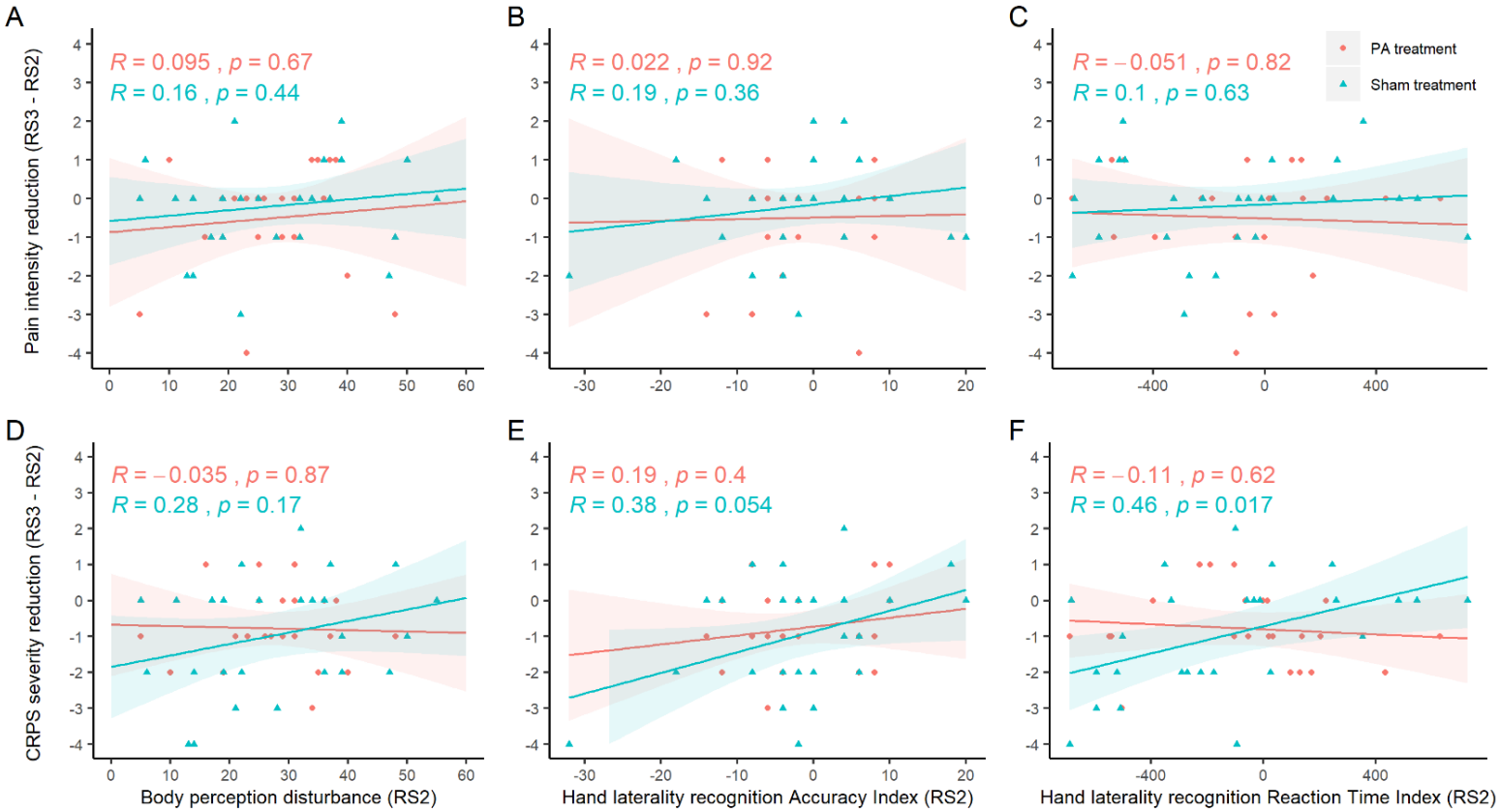

Figure 6. Scatterplots of changes on the primary outcomes vs. baseline scores on tests of body representation (intention-to-treat analysis). Relationships between individual participants' change in pain intensity (top panel) and CRPS severity (bottom panel) over the treatment period (between RS2, research session 2, and RS3, research session 3) and their baseline (RS2) scores on the Bath CRPS Body Perception Disturbance Scale (A, D), accuracy indices (B, E) and reaction time indices (C, F) on the Hand laterality recognition task are illustrated. Negative scores for pain and CRPS severity indicate reduction of these outcomes (i.e. improvement). Higher scores on Bath CRPS Body Perception Disturbance Scale and more positive indices of the Hand laterality recognition indicate greater disturbance of representation of the affected limb. Lines of best fit with confidence intervals (shaded surfaces) are superimposed for each treatment group. Pearson's correlation coefficients (R) are reported for the relationships between pain reduction (top panel) or CRPS severity reduction (bottom panel) and scores on tests of body representation. For pain reduction score, one observation was removed as an outlier (score = -7).

We also repeated the analyses of the primary outcomes including only those participants from ITT sample who showed reduced attention to their affected side in RS2. First, we selected participants who had negative PSS scores on the TOJ task (PA n = 13, Sham n = 13), because people with CRPS consistently showed spatial biases on this task in previous studies [12,21,77,78,90]. For this subgroup, a 2 x 6 ANOVA on current pain intensity did not reveal any significant interaction effect between Group and Time, $F(2.96, 71.02) = 0.42$, $p = .733$, $\eta^2_p = 0.02$, or any effect of Group, $F(1, 24) = 0.04$, $p = .841$, $\eta^2_p < 0.01$. Main effect of Time indicated that regardless of treatment, participants reported less pain from RS1 to RS2 ($p = .043$) and from RS2 to RS3 ($p = .026$), and more pain from RS4 to LTFU1 ($p = .025$), $F(2.96, 71.02) = 4.42$, $p = .007$, $\eta^2_p = 0.16$. These effects, however, would not withstand correction for multiple comparisons ($ps_{adj} \geq .202$). A 2 x 4 ANOVA on CRPS severity scores also did not reveal any significant interaction effect, $F(3, 72) = 0.72$, $p = .541$, $\eta^2_p = 0.03$. A significant effect of Group indicated that participants who received Sham treatment had more severe CRPS in RS2 ($p = .007$; $p_{adj} = .028$) and RS3 ($p = .039$; $p_{adj} = .114$) compared to those who received PA treatment, $F(1, 24) = 4.73$, $p = .040$, $\eta^2_p = 0.17$. There was also a significant effect of Time, indicating that regardless of treatment, participants' CRPS severity decreased from RS2 to RS3 ($p = .001$) and this reduction was maintained in RS4 ($p = .011$; $ps_{adj} \leq .033$), $F(3, 72) = 8.42$, $p < .001$, $\eta^2_p = 0.26$.

Next, we also repeated the same analyses on participants who had negative bias scores on the Greyscales task (PA n = 11, Sham n = 9), because performance on this task correlated with CRPS severity reduction scores (Figure 5). For this subgroup, a 2 x 6 ANOVA on current pain intensity did not reveal any significant main effects or interactions: Time, $F(5, 90) = 0.97$, $p = .443$, $\eta^2_p = 0.05$; Group, $F(1, 18) = 0.04$, $p = .842$, $\eta^2_p < 0.01$; Time x Group, $F(5, 90) = 0.80$, $p = .554$, $\eta^2_p = 0.04$. A 2 x 4 ANOVAs on CRPS severity scores did not reveal any significant effect of Group, $F(1, 18) = 0.01$, $p = .906$, $\eta^2_p < 0.01$, or interaction, $F(2.08, 37.36) = 0.17$, $p = .854$, $\eta^2_p < 0.01$. However, there was a significant effect of Time, indicating that regardless of treatment, participants' CRPS severity decreased from RS2 to RS3 ($p = .001$) and this reduction was maintained in RS4 ($p = .005$; $ps_{adj} \leq .015$), $F(2.08, 37.36) = 9.63$, $p < .001$, $\eta^2_p = 0.35$.

Finally, we repeated the analyses of the primary outcomes including only those participants from ITT sample who showed impaired laterality recognition of images of hands corresponding to participants' affected limbs in RS2, that is, had positive hand laterality recognition accuracy indices (PA = 7, Sham = 8). A 2 x 6 ANOVA on current pain intensity did not reveal any significant main effects or interactions: Time, $F(2.51, 32.59) = 0.45$, $p = .688$, $\eta^2_p = 0.03$; Group, $F(1, 13) = 2.54$, $p = .135$, $\eta^2_p = 0.16$; Time x Group, $F(2.51, 32.59) = 0.93$, $p = .423$, $\eta^2_p = 0.07$. A 2 x 4 ANOVAs on CRPS severity scores did not reveal any significant effect of Group, $F(1, 13) = 0.02$, $p = .881$, $\eta^2_p < 0.01$, or interaction, $F(3, 39) = 0.32$, $p = .815$, $\eta^2_p = 0.02$. There was a significant effect of Time, $F(3, 39) = 4.02$, $p = .014$, $\eta^2_p = 0.24$, consistent with a decrease in CRPS

severity regardless of treatment, however, follow-up contrasts revealed no significant differences between any time points (*ps* ≥ .065).

Overall, in line with the primary analysis of current pain intensity and CRPS severity, there were no interactions between Time and Group, even among participants with reduced attention to the affected relative to unaffected side, or those with distorted representation of the affected limb at baseline. The results of these exploratory subgroup analyses suggest that PA did not result in greater reductions in pain or CRPS severity than Sham treatment for those participants who showed baseline "neglect-like" bias or those who showed distorted body representation. However, note that the current study for not specifically powered to address these questions.

3.6. Predictors of CRPS progression over time

We explored which baseline factors (RS1) could predict overall change in pain intensity (across RS1-RS4 and LTFU1-LTFU2) and CRPS severity (across RS1-RS4). The identified best subsets regression models with respective values of model selection criteria are summarised in Table S2, Supplemental Material. A one-factor model for predicting overall change in pain intensity had the lowest AIC and CV criteria, $F(1, 46) = 5.46$, $p = .024$, *adj*. $R^2 = .09$, AIC = -132.24, CV = 0.28. In this model, greater reduction in pain intensity was best predicted by smaller change in hand preference since CRPS onset (absolute ΔEHI; $t = 2.34$, $p = .024$, $ß = 0.33$). For predicting overall change in CRPS severity, a three-factor model had the lowest AIC and CV criteria, $F(3, 45) = 6.23$, $p = .001$, *adj*. $R^2 = .25$, AIC = -55.52, CV = 0.55. In this model, greater reduction in CRPS severity was best predicted by lower pain intensity ($t = 3.69$, $p < .001$, $ß = 0.52$), less swelling of the affected limb ($t = 2.52$, $p = .015$, $ß = 0.37$), and more accurate recognition of images of the affected hand (i.e. smaller Hand laterality recognition accuracy index; $t = 2.43$, $p = .019$, $ß = 0.32$), as measured at baseline (RS1).

4. Discussion

The results from this double-blind, randomized, sham-controlled trial of PA for upper-limb CRPS-I do not support the hypothesis that the effects of PA and sham treatment differed. First, two weeks of twice-daily PA treatment performed with the affected arm did not reduce the primary outcomes of current pain intensity or CRPS symptom severity more than sham treatment of the same intensity and duration. Second, PA did not affect the secondary outcomes of self-reported CRPS-related and psychological functioning; sensory, motor, and autonomic signs of CRPS; or spatial cognition, motor function, and body representation.

Our findings contradict the conclusion of previous preliminary studies that PA could relieve pain and other symptoms of CRPS. In the first study of PA treatment for CRPS, two weeks of once-daily training resulted in 50% pain relief, and reduced oedema and skin discoloration in five patients [105]. In the second study, three weeks of daily PA effectively resolved one patient's

pain, reduced autonomic symptoms, and improved motor function [10]. In the third study, a shorter but more intense PA regimen (twice-daily for four days) resulted in 36% reduction of pain in seven CRPS patients [13]. In the two latter studies, its effects on pain were maintained for up to two weeks after discontinuing the treatment. While addressing the limitations of these previous small-sample, uncontrolled, unblinded studies, our robust trial showed no benefits of PA for CRPS beyond those of a control treatment. A small reduction in pain intensity immediately following PA (13% reduction) was not significantly greater than that observed after sham treatment (3% reduction). Similarly, there was an overall reduction in CRPS severity immediately after the treatment that persisted for four weeks, but it was present in both PA (7%) and sham (8%) treatment groups. Consistent across per-protocol and intention-to-treat analyses, these findings suggest that PA does not incur any greater benefit than sham treatment, and thus is not effective for treating CRPS.

The decrease in CRPS severity across both treatment groups could be explained by a placebo effect and/or general benefits of moving the affected limb. Meta-analysis of clinical trials found that placebo response can correspond to 1.84 point immediate post-treatment reduction in CRPS pain [61], or 0.65 reduction in chronic pain more generally (on a 0-10 scale) [38]. This effect might also be responsible for the reduction in CRPS severity found in our trial. Increased movement of the affected limb is a likely alternative explanation, because all participants performed the pointing task with their affected hand, regardless of which treatment they received. Physical exercise is one of the core pillars of CRPS management [27], and this additional daily activity might have been sufficient to reduce CRPS severity. Although there was no change in specific movement-related outcomes (except improved grip strength in the per-protocol analysis), movement itself could lead to adaptive engagement with the affected limb. It is unlikely that the observed changes were due to natural recovery, which might occur within the first year from diagnosis [2], as our participants were on average diagnosed with CRPS for five years (only 14% were diagnosed for ≤1 year). Disease duration was also unrelated to change in pain intensity or CRPS severity (see Figure S3, Supplemental Material). Regression to the mean cannot fully account for the decrease in CRPS severity, as no changes occurred over the baseline period. Overall, our findings reinforce the importance of including control treatment arms in pain rehabilitation studies, and the role of active movement in managing long-standing CRPS.

The absence of any effects of PA on clinical outcomes could be driven by the absence of any effects on spatial cognition and/or body representation. One hypothesised mechanism of the apparent benefits of PA treatment in previous studies of CRPS is that it reduces pain by correcting "neglect-like" spatial biases away from the affected side (although why such a lateralised bias would lead to or exacerbate pain is unclear). Research on prism adaptation in neurologically healthy individuals and in brain injured patients with hemispatial neglect demonstrated that the pointing after-effects of PA generalise to higher cognitive functions. Specifically, PA can induce

a shift in spatial cognition and motor control consistent with the direction of after-effect, that is opposite to the direction of lateral visual displacement [4,15,23,42,54,55,66,67,94,95,103]. A potential second mechanism for the apparent benefits of PA treatment for CRPS is restoring normal sensorimotor integration [10,105]. This is based on the proposal that distorted body representation gives rise to discrepancies between anticipated and actual consequences of movement, and these discrepancies cause or exacerbate pain in conditions such as CRPS [9,37,62,63]. The visual shift during PA induces transient sensorimotor incongruence that might provide an error signal that triggers normalisation of body representation. The two proposed mechanisms would predict that reduction in clinical symptoms following PA should be accompanied by normalisation of spatial cognition and/or body representation. In the present study, PA did not change participants' performance on experimental measures of spatial cognition and motor control, or body representation. This might explain why there were no therapeutic effects of PA.

It is possible that PA did not affect these neuropsychological functions because, in contrast to previous findings [12,21,24,26,78,89,90,99,104], our participants with CRPS did not have any systematic neuropsychological deficits. Despite relatively larger sample size and better methodological control, participants with CRPS in our study showed balanced distributions of spatial attention and spatial representations, no systematic slowing of movements directed towards the affected side, and unimpaired laterality recognition of images of affected hands at baseline (see Table 6 and Chapter 4, [31]). In healthy individuals, cognitive after-effects depend on baseline spatial bias [15,28,43]. Therefore, absence of pre-existing spatial bias might account for why PA had no effects on spatial cognition or motor control in the present study. Furthermore, if altering spatial cognition and/or body representation were integral mechanisms through which PA reduces CRPS symptoms, the lack of effect of PA on the primary clinical outcomes could be because of the absence of baseline neuropsychological deficits. However, below we discuss three reasons that do not support this explanation.

First, we found no relationships between the extent of baseline spatial and body representation deficits and changes in primary outcomes over the treatment period (Figures 4 and 5). Furthermore, sub-group analyses revealed no evidence that PA benefitted individuals who did present with "neglect-like" symptoms or distorted representation of the affected limb. Second, Christophe et al. [13] reported reduced CRPS pain after PA in the absence of any baseline spatial deficits, and without any effect on spatial cognition or motor control. Finally, Sumitani et al. [105] found a significant reduction in pain post-treatment, and a simultaneous shift in the coding of external spatial information relative to the body *away from* the affected side (i.e. in the direction opposite to the expected PA spatial after-effects). Therefore, response to PA treatment appears unrelated to "neglect-like" spatial bias or body representation distortion. However, both previous studies [13,105] had no control treatment arms, thus the apparent benefits of PA could be due to

other non-specific factors. Nonetheless, we dismiss the explanation that the reason why PA did not reduce pain or CRPS severity was because our participants showed no baseline deficits in spatial cognition or body representation, and thus PA could not normalise these cognitive functions. Rather, our findings suggest that PA is not an effective treatment for CRPS.

There are several potential limitations of the current study. First, we cannot rule out treatment compliance violations. We tested PA as a self-administered, home-based treatment that could realistically be integrated into CRPS management. Although participants received in-person training, written and video instructions, and both groups logged similar number of treatment sessions, we solely relied upon self-reported adherence. Lack of apparent difference between the effects of PA and sham treatment could potentially be due to deviations from the instructed treatment protocol. However, previous CRPS studies reported symptom improvement following less frequent [105], shorter [13], and home-based [10] PA, thus potentially missed treatment sessions should not disrupt the therapeutic effects of PA. Another limitation is that we did not measure whether the adaptation took place, which could potentially explain the lack of therapeutic effects of PA. The processes of realignment of spatial reference frames might be altered in individuals with CRPS, for instance due to impaired learning of spatial contingencies [8]. This question could be addressed by measuring the after-effect (e.g. through subjective straight-ahead) immediately after the initial PA training and upon completion of the treatment (i.e. in another supervised PA session immediately before RS3). Unfortunately, it was not feasible to confirm adaptation by measuring pointing after-affects in this trial due to scheduling issues, researcher availability and blinding, and equipment limitations for mobile use across research centres and participants' homes. Nonetheless, consistent with the prescribed regimen of each training session, 50 movements were sufficient to induce adaptation in previous studies [95]. A recent lab-based study from our research group suggested that although participants with CRPS adapt to lateral visual displacement at a slower rate than pain-free controls, the adaptation takes place in less than 50 rapid pointing movements, and the magnitude of after-effects does not differ between CRPS and pain-free participants (unpublished data). Therefore, the assumption that adaptation in the PA group did take place is plausible. Another factor that could potentially contribute to lack of therapeutic benefits of PA for CRPS is insufficient dosage of and exposure to treatment in the current trial. Our participants took less time to complete each treatment session (on average 2-3min) compared to post-stroke patients (20-30min) [23,100]. Furthermore, it was suggested that in people with hemispatial neglect, a minimum of 40 treatment sessions is needed to obtain significant, long-lasting functional benefits [45]. Thus, it is possible that 29 short PA sessions were not sufficient to induce long-term adaptation and realignment of sensorimotor frames in our CRPS participants. Yet it is noteworthy that in other studies, PA protocols similar to ours, using sufficiently strong prisms (10-20°) and 10 or more treatment sessions, found generalizable, long-lasting effects on hemispatial neglect [23,79,100]. Nonetheless, a trial of supervised PA with

longer exposure and evidenced adaptation might find a significant benefit for CRPS, in which case PA would be best integrated into more intensive in-patient pain management programs.

The longitudinal nature of this study allowed us to explore potential baseline predictors of CRPS progression over 10-30 weeks, regardless of treatment. Smaller change in hand preference since CRPS onset was related to greater reduction in pain intensity. Consistent with the learned non-use hypothesis [85], underutilization of CRPS-affected limb and compensatory use of the unaffected extremity might maintain CRPS symptoms and hinder recovery. Overall reduction in CRPS severity was predicted by smaller pain intensity and oedema of the affected limb, suggesting that people with milder symptoms are likely to improve more. Individuals who were better at recognising images of affected relative to unaffected hands also achieved greater reduction in CRPS severity. Body perception disturbance was previously linked to longer CRPS duration and more severe sensory and motor signs of CRPS [46,51,113]. Our finding that less distorted representation and maintained use of the affected limb predict greater symptom improvement support multidisciplinary pain management approaches and graded motor imagery, which aim to normalise body representation and foster active movement [27,75,76]. These interpretations are, however, tentative, as the analyses were exploratory and the abovementioned factors explained only 9% and 25% of variance in the overall changes in pain intensity and CRPS severity, respectively.

We conclude that PA does not reduce pain and other symptoms of CRPS more than sham treatment. The benefits of PA for CRPS reported in previous studies are likely due to the placebo effect, greater movement of the affected limb, regression to the mean, or natural recovery.

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Chapter 5 – Conclusions

This chapter addressed one of the main objectives of this thesis through testing whether prism adaptation treatment can reduce pain and severity of CRPS symptoms. The results of the first randomised controlled trial of prism adaptation reported in this chapter challenge the former positive findings by showing that prism adaptation has no therapeutic effects beyond those of sham treatment. Therefore, the present findings do not support recommending prism adaptation as a standard treatment for CRPS. Participants who underwent real prism adaptation reported an average reduction in pain of 0.78 points on a 0-10 scale, which is comparable to the size of placebo effect identified in clinical pain trials (Hróbjartsson & Gøtzsche, 2001). Although the direction of this change in pain intensity was consistent with pain relief following prism adaptation in previous studies, the reduction was not significantly greater than that reported by participants in a control group (0.19 points), leading to a conclusion that for pain intensity, there was no significant benefit of prism adaptation beyond sham treatment. In contrast to pain, CRPS severity significantly decreased over the treatment period; however, this reduction did not differ between the two treatment groups. Thus, the overall symptom improvement could either be attributed to increased movement of the affected limb, which was used to execute pointing movements in both real and sham treatment, or to the placebo effect. It is possible that the benefits of prism adaptation previously found in small, uncontrolled studies, occurred due to the same factors. The only control measure was implemented by (Sumitani, Rossetti, et al., 2007), who re-assessed one of their participants with CRPS after administering interventions equivalent to sham treatment. Specifically, this patient underwent two non-blinded periods of prism adaptation, once using neutral lenses, and once using lenses inducing lateral visual shift of 5°. Neither of these interventions produced any adaptation after-effects, and during both periods, the patient's average pain remained constant. This suggests that sham prism adaptation using neutral lenses is a valid control condition, and that prism adaptation reduced pain more than sham treatment for this individual patient (although lack of blinding prevents ruling out the placebo effect following active treatment). Thus, it is possible that prism adaptation could be beneficial for some individuals with CRPS, especially considering high individual variability in spatial biases demonstrated in Chapter 4.

Consistent with the findings presented in Chapter 4, participants with CRPS on average did not show any deficits in spatial cognition before treatment. Notably, as the primary clinical application of prism adaptation is to normalise spatial attention in hemispatial neglect after brain injury, it could be argued that if there were no attention deficits to begin with, changes in spatial attention would not lead to any improvement. As discussed in the conclusions of Chapter 4, this undermines the rationale for using prism adaptation treatment in CRPS, unless alternative mechanisms are involved. Yet similarly, if prism adaptation were to reduce pain through normalising body representation, in the absence of any baseline distortions, changes in body

representation would not yield therapeutic effects on clinical symptoms. However, based on further consideration of the data from this and previous studies, I disregarded the explanation that lack of therapeutic effects of prism adaptation in this trial could be due to the absence of baseline neuropsychological symptoms. Exploratory analysis did not identify any subgroups of individuals who responded to prism adaptation better than to sham treatment. Individual variation in spatial and body representation biases illustrated in Figures 5 and 6 closely resembled that presented in Chapter 4 (Figure 2), yet it was not related to the response to prism adaptation treatment. These findings do not support neither of the two proposed mechanisms of prism adaptation for the treatment of CRPS.

Regardless of treatment type, spatial cognition, motor control, and body representation appeared to remain stable over 2.5 months period in the present study, in contrast to the spontaneous reversal of spatial attention bias over 10 months in one single case of a patient with CRPS (Chapter 2). With high individual variation of cognitive biases in mind, such changes might have occurred in some participants. However, the drawbacks of using sensitive measures of multiple domains of neuropsychological functioning in this study include increased task difficulty and prolonged testing time (up to four hours per session). These factors could increase participants' fatigue, which in combination with potential side effects of pain medication, might have had a detrimental effect on cognitive performance (Boksem et al., 2005; Hart et al., 2000). That is, the sensitivity of the assessments and ability to detect changes in neuropsychological functioning over time and / or due to treatment could be reduced. This limitation should be considered when making conclusions about the stability of cognitive performance in CRPS.

On the other hand, it seems relevant to mention how remarkably well the participants coped with demanding assessments, long testing time, and engagement in the trial and the treatment itself, notwithstanding their pain and related symptoms. The quality of data was good, for instance, it was possible to fit psychometric functions to almost all participants' responses in the psychophysical tasks, and the overall loss of data was <1%. One exception was the spatially defined motor function task, in which up to 8% of data had to be removed across different analyses, mainly in the conditions completed with the affected limb. In that case, specific task demands were likely to be affected by the primary motor deficits. Despite the retention of only 76% of enrolled participants, pain and symptom severity of those who withdrew from the study did not systematically differ from the participants who remained. Out of those who completed the treatment and all the research sessions, 44% reported severe pain (≥7/10 points) and 98% presented with motor impairments on the affected side at baseline. Although some difficulties with carrying out the treatment using the affected limb would be expected due to pain evoked by movement and primary motor signs of CRPS, on average, participants completed the training considerably faster than it would normally take patients with hemispatial neglect. Overall, regardless of severe symptoms and continuous pain, participants seemed to manage the functional

impact of their condition relatively well, to the extent that allowed them to almost fully engage with the trial.

The limitations of the design of this trial raise a question as to whether different dosage, administration, and / or setting of prism adaptation would yield more favourable results. In order to maximise any potential effects of treatment, one could directly monitor participants' compliance with the prescribed treatment regimen, ensure that adaptation takes place by measuring immediate after-effect, increase the duration of prism adaptation sessions and the number of sessions itself (Kerkhoff & Schenk, 2012) to aid long-lasting realignment of sensorimotor frames, and / or use more goal-directed and ecologically valid tasks (Fortis et al., 2020) to facilitate generalisation of the effects of prism adaptation. Nonetheless, the current state of evidence does not support the effectiveness of prism adaptation for CRPS treatment. Further research on neurocognitive treatments for chronic pain could still be beneficial, provided that the theoretical or empirical basis of their mechanisms of action are demonstrated.

This chapter addressed another main objective of this thesis through investigating whether neuropsychological symptoms contribute to clinical manifestations of CRPS. Here I explored which baseline characteristics of participants (regardless of their treatment allocation) predicted how much their pain and CRPS severity changed over time. The main findings suggest that individual differences in baseline motor function and cognitive representation of the affected limb are relevant for long-term CRPS outcomes, even though limb laterality recognition was not impaired on a group level. The preliminary conclusions drawn from these results, consistent with those proposed in Chapter 4, are that improving motor function and re-establishing normal cognitive representation of the affected limb have potential to relieve pain and other symptoms. Summarising the findings from both chapters, among the tested neuropsychological functions, only body representation seems relevant for clinical features of CRPS. Additionally, primary motor impairment and underutilization of the affected limb, and bilateral deficits in motor control appear to determine the overall severity of the condition. Notably, both chapters suggest that changes in spatial cognition are not related to pain nor CRPS severity, or are, at least, less relevant than body representation and motor function.

Taken together, although this randomised controlled trial did not yield the expected results, the present findings bear significant contribution to understanding the role of neuropsychological functions in the manifestation and treatment of CRPS. The role of any changes in spatial cognition appears to be rather limited, whereas body representation emerges as potentially relevant symptom in the exploratory analyses. However, further studies would be needed to directly test these preliminary proposals. In the context of central mechanisms of CRPS, the present behavioural findings do not support the contribution of cortical reorganisation (particularly parietal networks) to clinical signs of CRPS.

General discussion

Pain cannot be explained or quantified solely by the severity of physical injury. Neuropsychological changes are thought to play a role in the clinical manifestation of chronic pain syndromes such as CRPS and have been regarded as an avenue towards better understanding of the central mechanisms of chronic pain and improving pain management. Twenty-five years of research has suggested that people with CRPS can present with neuropsychological changes in attention to and representation of their body and surrounding space, which to some extent resemble hemispatial neglect. In the absence of any observable brain pathologies, these neuropsychological symptoms could be consistent with functional cortical reorganisation. It has been suggested that cortical changes may be underlying pain conditions that lack obvious causal pathology, such as CRPS (Harris, 1999; McCabe & Blake, 2007). Furthermore, neurocognitive treatments that target neuropsychological symptoms have been used to reduce clinical symptoms of CRPS. This thesis examined (1) how neuropsychological functions are altered in CRPS, (2) whether neuropsychological symptoms contribute to the clinical manifestations of CRPS, and (3) whether prism adaptation treatment can reduce pain and other CRPS symptoms. This general discussion summarises the main findings and conclusions from these investigations, as well as their contributions to understanding and re-evaluating the role of neuropsychological changes in the manifestation and treatment of chronic pain.

Chapter 1 offered a novel way of looking into the central mechanisms of pathological pain: through changes in higher cognition. It significantly enhances the understanding of neuropsychological functions in CRPS based on the available evidence, including their relevance to clinical signs of the disorder and their treatment. The original contributions of this in-depth literature review are a comprehensive synthesis of the existing research findings regarding neuropsychological changes in CRPS, and discussion of their potential mechanisms. Furthermore, in this chapter, I highlighted inconsistencies in the available findings across different studies, and limitations in how certain cognitive functions have been defined and measured (e.g. the ambiguity between body representation distortions versus "neglect-like" symptoms), thus providing a useful resource for planning future studies. Notably, I addressed the identified limitations further in the thesis by conducting robust, well-controlled studies, and by drawing on broader hemispatial neglect literature to clearly dissociate spatial attention biases from body representation distortions.

Chapter 2 characterised biases in spatial attention in a single patient with CRPS over three research sessions. This longitudinal case study integrated methods and theoretical frameworks established in hemispatial neglect literature with cognitive experimental approach to behaviourally investigate potential functional changes in the brain. The findings provide a proof of principle that individuals with CRPS can have reduced attention to their affected relative to unaffected side of near space that is separable from attention in far space. The original

contribution of this study to the existing literature is demonstrating for the first time that the direction of spatial attention bias in CRPS might not be stable over time, and can be independent of pain severity and body representation distortion. The results also suggested that attention can be biased towards the painful side, which thus far has been reported in only one other case (Christophe, Delporte, et al., 2016; Jacquin-Courtois et al., 2017). These conclusions have potential implications for tailoring rehabilitation approaches to individual patients. They also demonstrate a disruption of cognitive functions typical of patients with brain lesions, but in the absence of any observable brain pathologies.

Chapter 3 presented the protocol for the major study of this thesis: the first trial to evaluate the effects of prism adaption versus control treatment on pain and symptom severity in a large sample of people with CRPS. In addition to clinical outcomes, this trial also examined the effects of treatment on neuropsychological changes to elucidate the working mechanisms of prism adaptation for CRPS. The participants' pain, psychological functioning, sensory, motor, and autonomic functions, and neuropsychological functions were tracked for up to 7.5 months to assess response to two-weeks of prism adaptation or sham treatment and CRPS progression over time.

Previous research found that people with CRPS can present with "neglect-like" symptoms. However, in Chapter 4, I comprehensively tested spatial cognition in a large cohort of people with CRPS and found no evidence for symptoms resembling perceptual, representational, or motor neglect. These findings do not uphold the analogy between hemispatial neglect and CRPS, but rather suggest that previously reported changes in spatial cognition might have been overstated. I also found no evidence for any clinical relevance of changes in spatial cognition for clinical signs of CRPS, thus challenging the assumed involvement of functional cortical reorganisation in the central mechanisms of the disorder. These results have further implications for potential neurocognitive treatments for chronic pain that target neuropsychological changes to reduce pain. For instance, they suggest that normalising spatial attention might not be the desired mechanism to target in order to reduce pain and other symptoms of CRPS. Chapter 5 indeed demonstrated that the effects of prism adaptation do not outweigh those of sham treatment. Thus, its major contribution is providing evidence base against recommending prism adaptation as a treatment for CRPS. The results of this chapter further suggest that even if prism adaptation did affect CRPS, it is unlikely that the mechanisms of such an effect would be attentional. Increased movement of the affected limb or placebo effect provide alternative explanations of previously reported reduction in pain and other symptoms following prism adaptation, and a decrease in CRPS severity over the treatment period in our trial regardless of real or sham prism adaptation. Indeed, findings from both Chapters 4 and 5 suggest that motor function could be an important predictor of clinical outcomes of CRPS. Among the tested neuropsychological functions, body representation showed potential clinical relevance, but spatial cognition did not.

The overarching question posed in this thesis concerns the role of neuropsychological changes in the manifestation and treatment of chronic pain. The overall conclusions and broader implications of the presented theoretical and empirical investigations of CRPS to address this question can be integrated according to the three main objectives of this work.

People with CRPS do not show systematic "neglect-like" symptoms

Integrating the findings from this thesis with the existing literature, our knowledge of the nature and prevalence of neuropsychological changes in CRPS is still limited, yet the present research provides some clarification. Here I did not replicate "neglect-like" symptoms that were repeatedly reported in previous studies. Having tested a large CRPS cohort, using robust, sensitive methods, these null findings suggest that previously reported changes in spatial cognition might have been overstated. An important factor to consider is individual variability that in some of the previous, small sample studies could have induced a selection bias towards individuals with pronounced cognitive symptoms. Heterogeneity of clinical manifestations of CRPS is well established and reflected in the diagnostic criteria (Bruehl et al., 2016; Harden et al., 2010; Marinus et al., 2011). If it were not for the fact that most participants with CRPS did not show any spatial biases in the studies reported in Chapters 4 and 5, it could be argued that similar heterogeneity characterises neuropsychological symptoms. For instance, there were some individuals with CRPS who, relative to healthy controls, clearly deviated either away from or towards their painful side, similar to the single patient described in Chapter 2. However, this observed individual variability in neuropsychological changes might have limited utility for explaining clinical symptomatology or potential treatment stratification. Based on the presented empirical findings, the extent or direction of any deficits in spatial cognition does not seem to be related to the severity of CPRS symptoms or response to prism adaptation treatment.

Challenging the presence of neuropsychological deficits in CRPS has implications for understanding its proposed mechanisms. From the perspective of chronic pain as a disease of the central nervous system, neuropsychological symptoms can be taken as behavioural indicators of functional reorganisation of cortical networks involved in higher cognitive processes. Resemblance of the previously reported "neglect-like" symptoms for the CRPS-affected side (Förderreuther et al., 2004; Galer & Jensen, 1999; Kolb et al., 2012; Reinersmann et al., 2010, 2012) to hemispatial neglect suggested that they might be associated with functional changes within the posterior parietal and temporal cortical networks that are usually disrupted in neglect after a stroke (Chechlacz et al., 2012; Molenberghs et al., 2012; Mort et al., 2003; Vallar, 2001). My findings challenge this proposal, as they show no evidence of any systematic deficits across multiple sensitive measures of spatial cognition in a large cohort of people with CRPS. Absence of consistent behavioural indicators of reorganisation within the cortical networks governing spatial cognition suggests that CRPS is probably not associated with altered higher-order cortical representations. Neuroimaging evidence of any functional changes in the parietal cortex in people

with chronic pain is scarce (see Chapter 1). However, in light of the current null findings and the previous conflicting literature, this paucity of evidence does not necessitate further research aiming to identify neural correlates of neuropsychological changes in CRPS, unless consistent and systematic behavioural evidence of such changes emerges (Krakauer et al., 2017).

In the context of broader neuroplasticity in CRPS, even seemingly well-established evidence of shrinkage of the primary somatosensory representation of the affected hand (Di Pietro et al., 2013b) has been recently disputed (Mancini et al., 2019), further suggesting unaltered cortical representations. In the studies presented in this thesis, participants with CRPS did report distorted perceptions of and negative feelings towards their CRPS-affected limb. Unfortunately, lack of available validation of the self-report measure of altered body representation (Lewis & McCabe, 2010) limits our understanding of which exact sensory, cognitive, and / or emotional functions the patients' responses reflect. Furthermore, despite on average higher scores on the Bath CRPS Body Perception Disturbance Scale compared to pain-free individuals, these responses of the CRPS participants did not correspond to any biases in a more objective experimental measure of body representation, that is, hand laterality recognition (see Chapter 5). Although a meta-analysis found that people with chronic musculoskeletal pain affecting the limbs or face showed altered performance on laterality recognition tasks (Breckenridge et al., 2019), the evidence of deficits specific to the cognitive representation and motor imagery of the affected limb in CRPS has been highly inconsistent (see Chapter 1). Nonetheless, commonly reported subjective distortions of the representation of the CRPS-affected limb cannot be disregarded, thus further research could investigate what aspects of body perception are indeed affected in CRPS and develop robust methods to quantify them.

While in this thesis I specifically focused on spatial cognition and body representation, investigations of other neuropsychological functions in CRPS received relatively little attention. Impaired executive functions, deficits in working memory, psychomotor speed, or attentional capacity seem to affect people with chronic pain regardless of its location or diagnosis (Berryman et al., 2014; Hart et al., 2000; Landrø et al., 2013). Consistent with these findings, over 40% of people with CRPS presented with impaired executive functions, independent of medication use or mood disturbance (Libon et al., 2010). Aside from investigating neuropsychological changes that are thought to be specific to CRPS and elucidate its cortical mechanisms, further research could pursue the functional impact of chronic pain on cognitive processes determining, for instance, ability to work in these patients. The potential effects of medication or comorbid depression on cognitive functions have rarely been controlled for in CRPS research, and these factors could further be addressed via multidisciplinary interventions to achieve functional improvement, with potential implications not limited to CRPS.

Changes in spatial cognition or spatially-defined motor function do not contribute to clinical manifestations of CRPS

The findings summarised in Chapter 1 suggested that larger spatial biases might be related to more severe pain and other CRPS symptoms, yet the evidence was mixed. In this thesis, I investigated the potential predictors of pain intensity and CRPS severity and their progression over time. My findings suggest that the extent or direction of any spatial biases in visual attention, representation of space, or motor function is not related to the severity of clinical symptoms of CRPS or its long-term outcomes, and that the direction of spatial attention bias can change independently of CRPS pain. However, these insights were gained through exploratory analyses, thus, the conclusions are tentative and should be taken as indicating hypotheses that could be tested in future studies. Overall, my research indicates that "neglect-like" symptoms do not seem to contribute to the clinical manifestations of CRPS, adding to the share of previous studies that also found no relationships between these factors. The present negative findings do not exclude the possibility that clinical manifestations of CRPS might be partly driven by neuropsychological changes other than those related to spatial cognition. Further exploratory analyses revealed potential clinical relevance of distorted body representation (although limited by the measurement method and inconsistency between different tests of this construct).

The notion of cortical mechanisms underlying chronic pain greatly relies on previous research suggesting that reorganisation of somatosensory and motor cortical maps in CRPS, phantom limb pain, fibromyalgia, and nonspecific low back pain was related to pain severity (Flor et al., 1995, 1997; Henry et al., 2011; Karl et al., 2001; Kim et al., 2015; Maihofner et al., 2003; Pleger et al., 2006). Conversely, another study suggested that specific pathology, such as deafferentation or increased constant somatosensory input, rather than chronic pain itself, might be driving cortical plasticity (Gustin et al., 2012). Associations between pain severity and the extent of reorganisation of somatosensory cortex have been further debated in more recent studies that used robust neuroimaging methods accounting for individual cortical morphology. Specifically, Makin and colleagues (2015) found smaller than previously reported (and likely use-dependent) spatial shifts near the representation of the amputated hand in people with phantom limb pain. Mancini and colleagues (2019) found unaltered representation of the CRPS-affected hand. In both cases, individual differences in the size or spatial organisation of these maps were not related to participants' pain intensity. Although distorted cognitive representation of the affected limb reported by individuals with CRPS has been related to greater pain intensity and worse long-term outcome for symptom severity (Chapters 4 and 5), and previously taken as evidence supporting cortical mechanisms of the disorder (Lewis & Schweinhardt, 2012; Moseley, Gallace, & Spence, 2012), somatosensory information is not the sole component upon which a representation of one's body is built (Head & Holmes, 1912; Tsakiris, 2010). Thus, such distorted cognitive representation of the affected limb is plausible in absence of somatosensory cortical changes.

With regard to motor cortical reorganisation, a meta-analysis of neuroimaging studies in CRPS revealed limited evidence of bilateral disinhibition of the primary motor cortex, but no systematic changes in spatial motor representations (Di Pietro et al., 2013a). A meta-analysis of similar evidence in various chronic pain populations found that motor cortex disinhibition was most prominent in CRPS and neuropathic pain, compared to migraine or musculoskeletal conditions such as low back pain or fibromyalgia (Parker et al., 2016). However, this evidence does not allow to determine whether cortical disinhibition arises due to chronic pain, or whether it facilitates persistent pain. In the context of previous neuroimaging studies, bilateral motor slowing described in Chapter 5 could stem from reorganisation within the central motor networks. That is, if we assume that cortical reorganisation underlies CRPS pathology. However, movement slowing could just as well be related to decreased psychomotor speed found in a variety of chronic pain conditions, like diabetic neuropathy with predominately cardiovascular, in contrast to cortical, mechanisms (Higgins et al., 2018). In this thesis, the extent of motor deficits and the functional change in the use of the affected limb since CRPS onset were associated with greater pain intensity and CRPS severity, and worse long-term outcomes in these important clinical indicators. Thus, motor function appears to play an important role in the severity and maintenance of CRPS symptoms. Although we cannot exclude the contribution of disrupted central motor networks, the role of motor function can be partly explained via lower-level motor impairment and learned behaviour such as underutilisation of the affected limb.

Beyond the primary sensory and motor representations, my results contribute behavioural evidence to challenging the role of higher-order cortical reorganisation in the manifestation of CRPS. That is, individual variability in the performance on the tests of spatial cognition was unrelated to the severity of pain and other CRPS symptoms. This contrasts the idea that cortical plasticity within parietal and temporal networks might be contributing to CRPS pathology. It is worth noting, however, that central mechanisms of chronic pain are not limited to the assumed cortical reorganisation but can involve other processes such as central sensitisation on the spinal level, or descending pain modulation on supraspinal level, including subcortical structures. Nonetheless, the present findings call for reconsideration of the cortical mechanisms underlying chronic pain and rationale for treatments designed to normalise distorted cortical representations.

Prism adaptation is not an effective treatment for CRPS

One of the most important contributions of this thesis is to show that prism adaptation was not more effective in reducing pain and CRPS severity than control treatment in a double-blind randomised controlled trial (Chapter 5). Pain reduction after real prism adaptation was smaller compared to the preliminary studies (Figure 1). This is not surprising considering that effect sizes get smaller with increasing sample size (Button et al., 2013), which was much larger in the present trial. However, the facts that this pain reduction was neither significant nor greater than that observed following sham treatment, and that CRPS severity improved over time regardless of real

or sham treatment, suggest that previously reported positive effects of prism adaptation occurred due to other factors. Likely alternative explanations are increased movement of the affected limb, which would be supported by the clinical relevance of motor function discussed above, or the placebo effect, which can reflect a significant therapeutic response to non-active treatment conditions (Hróbjartsson & Gøtzsche, 2001). Meta-analyses of randomised controlled trials for chronic pain reported that, for instance, higher expectations of treatment efficacy, larger number of in-person research visits, or relatively larger active treatment group size are associated with greater placebo response (Linde et al., 2007; Vase et al., 2015; Zhang et al., 2008). The trial reported in Chapter 5 was double-blind, thus participants' outcome expectations, which were similar at baseline, could have remained high regardless of treatment allocation. No signs of superiority of prism adaptation over sham intervention highlight the importance of including control treatment arms in chronic pain trials.

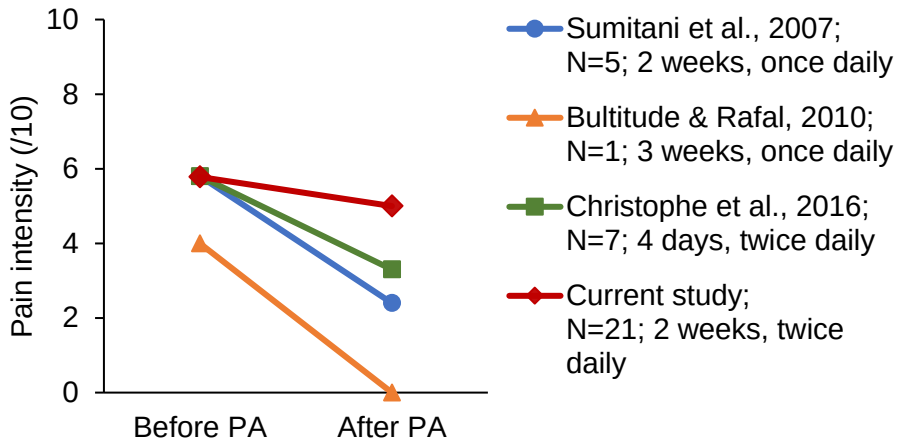

Figure 1. Pain reduction following prism adaptation treatment. Change in pain intensity after prism adaptation (PA) treatment reported in three previous studies and in the current trial are summarised. Pain intensity is expressed on an 11-point Numerical Rating Scale: 0 = "no pain at all", 10 = "the worst pain imaginable" used by Sumitani, Rossetti, et al. (2007), Bultitude and Rafal (2010), and in the current study; average ratings from a 0-100 Visual Analogue Scale with the same anchors used by Christophe, Chabanat, et al. (2016) were scaled for the purpose of comparison with the other studies.

In the present study, prism adaptation also did not affect other clinical signs of CRPS, neuropsychological symptoms, or self-reported psychological functioning. Importantly, although participants on average did not show "neglect-like" symptoms, prism adaptation also did not improve pain or CRPS severity more than sham treatment for those individuals who did present with reduced attention to their affected side or distorted body representation at baseline. Therefore, the present findings do not support the attentional or body representation mechanisms of the effects of prism adaptation on pain, and suggest that prism adaptation does not have greater therapeutic benefits for upper-limb CRPS-I than a control treatment. They also provide no indication that prism adaptation might be effective for a subgroup of individuals presenting with neuropsychological deficits.

The empirical research presented in this thesis has overall shown that spatial cognition biases do not seem to relate to clinical manifestations of CRPS, and targeting them using prims adaptation does not reduce pain. These behavioural findings suggesting rather limited role of neuropsychological changes or cortical reorganisation in the manifestation and treatment of CRPS challenge the utility of neurocognitive rehabilitation for this disorder. In particular, treatments that aim to relieve chronic pain via normalising cortical representations do not seem justified considering lack of consistent evidence of neuroplastic changes. However, given the preliminary evidence for links between clinical symptoms and motor function and body representation reported in Chapters 4 and 5, these domains might be more fruitful avenues for therapeutic investigations. Two related neurocognitive interventions for CRPS aim to normalise sensory-motor integration and body representation. In mirror visual feedback therapy (Ramachandran & Rogers-Ramachandran, 1996), patients execute synchronous bimanual movements, while viewing the movement of the unaffected limb reflected in the mirror creates an illusion that the affected extremity placed behind the mirror is executing identical movements despite motor impairment. The therapeutic mechanism of mirror therapy is thought to rely on re-establishing the congruent relationship between motor intention and sensory feedback. It has been hypothesised that discrepancy between these two processes can cause or exacerbate pain in CRPS (Brun et al., 2019; McCabe & Blake, 2007), although direct evidence supporting this mechanism is lacking. There is limited evidence of the effectiveness of mirror therapy for acute CRPS (McCabe, 2002), and in combination with exercise and medication (Kotiuk et al., 2019). Since mirror therapy might not be tolerated by some patients due to movement-related pain, Moseley (2004a) preceded it with hand laterality recognition training, and then imagined hand movements. Based on behavioural findings, these two stages are thought to sequentially activate cortical motor networks and reduce pain, thus facilitating commencement of mirror therapy (Moseley, 2005b). These mechanisms are, however, debatable, as laterality recognition of the affected relative to unaffected limb might be unimpaired in people with CRPS (Chapter 5; Breimhorst et al., 2018; Reinersmann et al., 2012). Nonetheless, graded motor imagery consisting of these three stages decreased pain and oedema, and improved limb laterality recognition in three randomised trials form the same research group (Bowering et al., 2013; Moseley, 2004, 2005b, 2006), yet it failed to reduce pain when applied in clinical practice (Johnson et al., 2012). Further research could pursue explaining the mechanisms of mirror visual feedback and graded motor imagery and refining their clinical applications. Notably, it is conceivable that their effectiveness does not necessitate simultaneous cortical reorganisation, and instead might rely on the improvement of motor function, which emerged as an important determinant of other clinical outcomes in the studies presented in this thesis.

In light of largely intact neuropsychological functions, rather than targeting areas of dysfunction, we could use unaffected cognitive abilities to aid rehabilitation of CRPS. For instance, people with CRPS appear to experience a normal rubber hand illusion (Reinersmann, Landwehrt, et al.,

2013), suggesting intact multisensory integration. The illusion occurs when watching an artificial limb being stroked, while one's own unseen limb is stroked in synchrony. This causes participants to have the impression of "feeling" the tactile sensations that are being applied to the artificial limb, as if it belonged to their own body (Botvinick & Cohen, 1998). Hence, inducing the rubber hand illusion might enable patients to observe the artificial limb being touched with textures or objects that would normally induce painful sensations on their affected limb. This could allow them to gradually learn to tolerate real touch on the painful limb, and thus reduce allodynia. Another potential avenue for treatment that could make use of intact multisensory integration involves manipulating auditory feedback anchored to one's movement, for example, during exercise of the affected limb. Tajadura-Jiménez, Cohen, and Bianchi-Berthouze (2017) showed that people with CRPS can adapt their walking to altered auditory feedback of their footsteps. Therefore, a form of auditory-motor adaptation could be used to improve movement of the affected limb.

Given the preliminary evidence of the contribution of active movement and maintained use of the painful limb to reduced severity of CRPS (Chapters 4 and 5), underutilisation of the affected limb could be addressed via more conservative treatments. It has been suggested that this behaviour in CRPS develops through operant conditioning, similar to underutilisation of the contralesional limb after a stroke (Punt et al., 2013; Taub et al., 2006). This learning-based hypothesis of motor impairment in CRPS fits within the contemporary fear-avoidance model of chronic pain (Vlaeyen & Linton, 2000). According to this model, the pathway to underutilisation of the affected limb leads from pain, through pain-related fear, to persistent avoidance behaviours that maintain the pain and disability in the long-term. Following from this model, exposure-based treatments that aim to extinguish pain-related fear were found to reduce pain and disability in CRPS (Barnhoorn et al., 2015; de Jong et al., 2005; den Hollander et al., 2016; Ek et al., 2009). Behavioural exposure therapies could potentially reverse learned underutilisation and restore motor function in a subgroup of people with CRPS who report high pain-related fear. It is curious that in the present studies, pain-related fear of movement was not related to the extent of motor dysfunction or CRPS severity. This could indicate that underutilisation of the affected limb is maintained through other factors, such as primary motor symptoms of CRPS. In this case, these symptoms might need to be alleviated through other therapies (e.g. pharmacotherapy) before commencing exposure treatment.

Another important therapeutic consideration is generalised functional impact of rehabilitation, even if substantial pain and symptom relief is not feasible. Prism adaptation investigated in this thesis involved monotonous, repetitive pointing movements. While its effects on hemispatial neglect were found to carry over to unexposed sensory, motor, and cognitive functions (Jacquin-Courtois et al., 2013), generalisation of the results of such training to distinct clinical symptoms of chronic pain and their functional impact might be limited. For instance, prism adaptation

treatment reported in Chapter 5 had no effects on self-reported pain interference, defined as detrimental impact of pain on daily life. A recent study assessed a modified ecological home-based prism adaptation training, in which patients with chronic hemispatial neglect performed daily sessions of scheduled activities involving manipulation of simple everyday objects, and free activities related to their hobbies and daily tasks, while wearing prism goggles. Two weeks of such training had comparable effects on neglect as traditional prism adaptation, and its benefits additionally extended to long-lasting improvement in patients' daily function (Fortis et al., 2020). Although prism adaptation does not appear to be an effective treatment for chronic pain, ecological approach to physiotherapy that involves everyday activities and aims to achieve specific functional goals could facilitate adherence to treatment and generalisation of any therapeutic effects to daily functioning. Indeed, individualised goal setting is the key element of pain management programmes, such as an exemplary programme described in Chapter 2 in the context of potentially reversing spatial attention bias in one CRPS patient. Multidisciplinary approach to treatment of CRPS (Goebel et al., 2018) utilizes pharmacotherapy, patient education, exercise and psychological interventions aimed at fostering acceptance and decreasing adverse feelings towards the affected limb. It further addresses counter-productive patterns of behaviour that might perpetuate disability, and aims to restore pre-CRPS level of daily functioning via graded activation guided by patients' goals. Although such programmes appear to be effective in clinical experience, further research should be undertaken to identify their specific active components and working mechanisms. This could facilitate broader implementation of relevant therapeutic techniques beyond the few specialised clinics. Nonetheless, the described principles are largely consistent with evidence-based guidelines for management of chronic pain more generally (Sanders et al., 2005; The British Pain Society, 2013).

Considering high heterogeneity of clinical presentations of CRPS, therapeutic decision-making could implement stratified approach, that is, target treatments to subgroups of patients based on their distinct characteristics, such as risk of persistent disability, hypothesised underlying mechanisms, or likely responsiveness to treatment. For instance, pharmacotherapy for neuropathic pain can be stratified according to the patients' sensory profiles (Baron et al., 2012), or type of physiotherapy for back pain can be chosen based on the patients' estimated prognosis (Hill et al., 2011). Since subgroup analyses reported in Chapter 5 failed to identify the responders to prism adaptation treatment based on patients' cognitive profiles, this strategy might not necessarily apply to neurocognitive interventions. However, people diagnosed with CRPS may present with strikingly different combinations of symptoms, for example, predominance of motor deficits, autonomic changes, or positive sensory signs. It would seem reasonable to place greater emphasis, respectively, on physiotherapy, anti-inflammatory medication, or desensitisation and centrally acting analgesics for these groups of patients. To facilitate such stratified approach, multiple research centres could combine their efforts in describing and understanding potentially distinct clinical profiles in a broader population of people with CRPS.

Taking into account the existing treatments for CRPS, the prognosis is still poor (Bean et al., 2016; de Mos et al., 2009). Based on the findings presented in this thesis, neurocognitive treatments targeting neuropsychological symptoms or cortical reorganisation might not be the best way forward. Instead, future research could focus on improving and evidencing the efficacy of the available treatments through high-quality randomised controlled trials and clarifying their mechanisms of action. Importantly, not all patients will respond equally to the same interventions, likely due to diversity of their symptoms. Thus, stratified approach targeting heterogeneous clinical presentations is likely to advance the management of chronic pain.

Final conclusions

To summarise, the predominantly null findings of this thesis regarding the hypothesised "neglect-like" symptoms in CRPS provide important information in the context of increasing interest and emerging research on the central mechanisms of CRPS, including cortical reorganisation and associated cognitive changes. Considering the methodological strengths of the presented empirical studies, the null results demonstrate that lateralised spatial biases are not a substantial part of cognitive symptomatology in CRPS. This conclusion endorses a more balanced perspective on changes in spatial cognition (or lack of thereof) in CRPS. It is unlikely that cortical reorganisation contributes to the manifestation or treatment of this disorder, which prompts reconsideration of the cortical-centred explanations of chronic pain more generally. The potential clinical relevance of body representation and motor function demonstrated in previous literature and the empirical studies of this thesis implies that deficits in these domains could be targeted for treatment of CRPS. This could be through exposure therapies, goal-directed physiotherapy, and multidisciplinary treatments, with emphasis on stratified pain management. In contrast, present research provides robust evidence that prism adaptation hypothesised to reduce pain through normalising spatial attention biases does not incur therapeutic benefits on CRPS compared to a control treatment.

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Appendix

Chapter 2 - Supplemental Material

Attention upturned: Bias toward and away from the affected side of the body and near space in a case of Complex Regional Pain Syndrome

1. Equipment

We used the following equipment for the experimental and sensory tests that involved presentation of visual stimuli on a computer screen. For the presentation of the Greyscales task in near and far space in T2, a 109.5 x 62.0cm size, 1920 x 1080 pixels resolution computer screen mounted on a wall was used. A desktop computer screen (47.5 x 26.7cm size, 1024 x 768 pixels resolution) was used for Freiburg visual acuity test and Global-local tasks in T2, and for the Perimetry, Landolt C, Greyscales, and Global-Local tasks in T3. A chin-rest was used for all vision tests and experimental tasks except the Greyscales task in T2, and was adjusted so that the participant's eye level was aligned with the central fixation cross.

2. Somatosensory testing: tactile detection and discrimination

2.1. Method

In T3, we assessed Mechanical Detection Thresholds (MDTs) on the participants' hands (centre of dorsal surface) and knees (centre of kneecap), using von Frey filaments of 0.008g to 300g force (Bioseb, model Bio-VF-M). The procedure followed a standardised protocol from Quantitative Sensory Testing (Rolke et al., 2006).

We assessed tactile discrimination thresholds on the participants' index fingers and knees using a Two-Point Discrimination disk (TPD; Exacta, North Coast Medical) in T3. The participants reported if they perceived the touch on one point or two points on the centre of their index fingertip or the centre of their kneecap. The researcher touched the participant's skin with one or two tips of the disk simultaneously, decreasing (down to a single tip) or increasing (up to 20mm) the distance between the two tips according to a staircase procedure. We calculated TPD threshold as a geometric mean of ten turning points on each hand / knee.

We derived relative threshold ratios as [(left - right) / left], separately for each measure (MDT and TPD) and each testing location (hands and knees). The results represent the difference in tactile sensitivity (MDT) / discrimination (TPD) on the left side compared to the right side, as a proportion of overall tactile sensitivity / discrimination on the left side. Negative numbers indicate lower thresholds (thus higher sensitivity to touch / more precise discrimination) on the left (affected) side.

3. Temporal Order Judgement task - Just Noticeable Difference

3.1. Method

We calculated half the temporal interval between the 25% and 75% points on the psychometric function to derive Just Noticeable Difference (JND). JND is a measure that indicates the delay between the two stimuli needed for the participants to perceive the correct order of the two stimuli at a specified level. JNDs were also averaged across Response conditions and subjected to the same analyses as Points of Subjective Simultaneity (PSSs).

3.2. Results & conclusions

The patient had significantly larger JNDs than controls in TOJs of visual stimuli presented in her body space in T2 (JND = 202.98), $t(11) = 4.05$, $p < .001$, $z_{cc} = 4.212$, 95% CI [2.381, 6.028], and in hands working space in T1 (JND = 144.93), $t(23) = 2.25$, $p < .05$, $z_{cc} = 2.296$, 95% CI [1.518, 3.061], T2 (JND = 268.53), $t(11) = 4.56$, $p < .001$, $z_{cc} = 4.744$, 95% CI [2.704, 6.770], and T3, (JND = 103.16), $t(11) = 2.53$, $p < .05$, $z_{cc} = 2.633$, 95% CI [1.398, 3.845]. This suggests that the patient was less precise in judging the temporal order of visual stimuli in these conditions, relative to healthy control participants. No significant differences in JNDs were found when visual stimuli were presented in near space on eye level, or when tactile stimuli were delivered to participants' lower limbs.

Due to insufficient variability in the patient's responses across different temporal offsets, we were not able to fit the cumulative Gaussian to determine the JNDs in Uncrossed Hands condition in T1, and Crossed Hands conditions in T1 and T2. It appears that the patient was not able to make reliable perceptual judgements in the conditions which could be associated with increased cognitive or emotional difficulty, stemming from conflicting left/right information (incongruence between the two sides of the body and external space), and focusing on the information appearing on the CRPS-affected part of the body. Achieving a reliable pattern of responses that allowed fitting cumulative Gaussian in Uncrossed Hands condition in T2 could be attributed to using longer temporal offsets between the stimuli compared to T1. Nevertheless, the procedural adjustments were not sufficient to provide reliable data in Crossed Hands condition in T2.

4. Global-Local Processing task

To determine if the left inattention that we observed in the CRPS patient in T1 was accompanied by cognitive symptoms indicative of broader changes to right hemisphere function, we used Global-Local Processing tasks in T2 and T3 to assess whether she showed a local processing bias compared to healthy controls. We also aimed to test whether any local processing bias would be limited to or stronger in the CRPS-affected side of space (left visual field) or present in both sides of space. In general, control participants show a tendency for prioritising global configurations relative to local features (Heinze & Münte, 1993; Navon, 1977; Pomerantz, 1983; Proverbio,

Minniti, & Zani, 1998). This can be measured in the form of faster and / or more accurate performance when identifying global configurations compared to local features (global precedence). It can also be seen as less interference from incongruent local level information when identifying global configurations (local interference) compared to the interference from the global configurations when identifying local features (global interference). We hypothesised that, compared to controls, the patient would show significantly lower global precedence, lower global interference, higher local interference, and a higher ratio of local to global interference.

4.1. Method & results (T2)

The stimuli and procedure were similar to those described in a previous paper (Bultitude, Rafal, & List, 2009). We used hierarchical stimuli (Navon letters; Navon, 1977) of small letters (0.40° x 0.60°) that formed the shape of the same (congruent) or a different (incongruent) larger letter (2.50° x 3.80°). Participants were required to identify either Global (large letters) or Local (small letters) level of the stimuli in two separate blocks (Target Level conditions). In each trial, a black fixation cross (0.57° x 0.57°) was displayed in the centre of a white screen. After 1000ms it was joined by one of the hierarchical stimuli, with its centre located 3.65° to the left or right of the fixation cross. The stimulus was presented for 100ms. Participants were instructed to press the "up" arrow key if they identified the local / global stimulus as A, and the "down" arrow key if they identified an S. Each trial ended with the participant's response or after a time out period of 4000ms since the stimulus onset. Both speed and accuracy were emphasised in the instructions. Each of the four types of stimuli (two congruent and two incongruent) was presented 16 times in the left (LVF) and in the right visual field (RVF), giving 128 trials per condition. Each Target Level condition block was preceded by eight training trials.

We analysed accuracy rates (Figure S1) and mean reaction times (Figure S2) for congruent and incongruent stimuli in Global and Local conditions, separately for each visual field. The analysis plan to derive global precedence, local interference, global interference, and global-local processing bias indices was described in the preregistration record (osf.io/zx8ad).

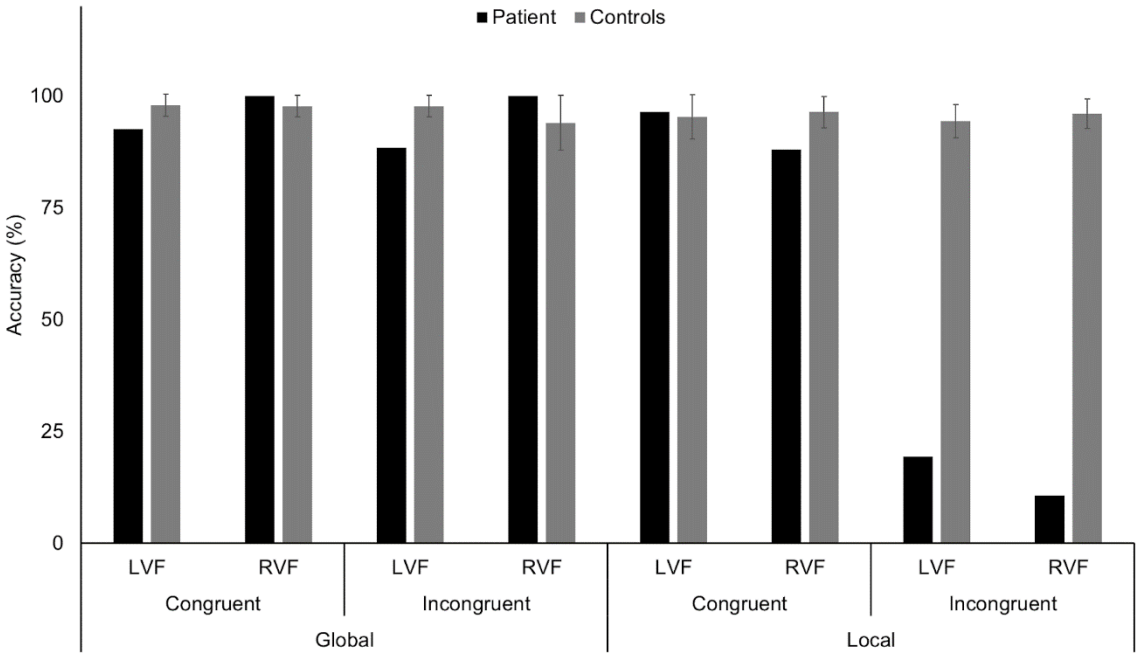

Figure S1. Global-Local Processing task (T2) – accuracy. The patient's and controls' mean accuracy rates (%) for congruent and incongruent stimuli in left and right visual field (LVF and RVF, respectively) in T2. Error bars represent standard deviations of the controls' means and are not presented for the patient's single accuracy rates.

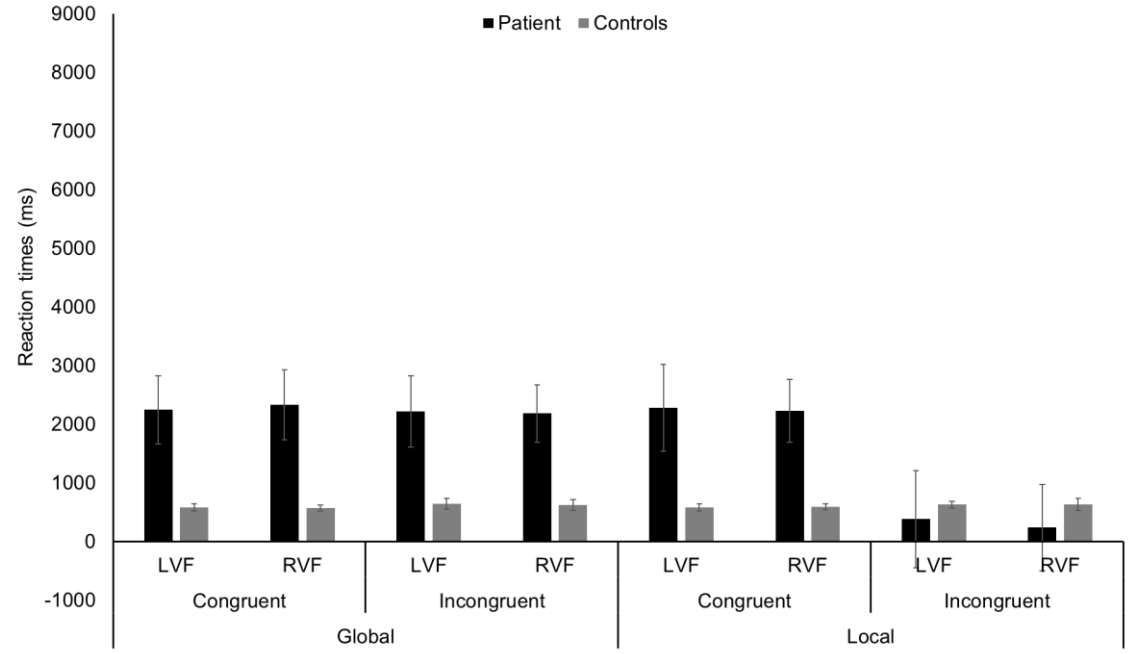

Figure S2. Global-Local Processing task (T2) – reaction times. The patient's and controls' mean reaction times (ms) for congruent and incongruent stimuli in left and right visual field (LVF and RVF, respectively) in T2. Error bars represent between-subjects standard deviations of the controls' means and within-subject standard deviation for the patient.

The results from T2 showed that the patient had low accuracy rates for incongruent stimuli in the Local condition (< 20% correct; 20 standard deviations below the mean of the controls; see Figure S1). Since this is lower than chance-level performance (50%), this suggests that she was mostly

responding to global features throughout the Local block. This could be explained by severe global processing bias (tendency to process the global form rather than the local level), or by perseveration (as the Global block was conducted first). However, we consider these two possibilities to be unlikely due to further information: of those Local Congruent trials that were correct (6/32 in LVF and 3/32 in RVF), the reaction times were very fast compared to other conditions (Figure S2), suggesting that she was not making a true discrimination judgement on these trials. This, coupled with the patient's report of poor peripheral vision, led us to believe that the stimuli were too small for the patient to be able to visually process and discriminate the local level and do the task as instructed. Thus, conducting the full planned analysis on these data would be uninformative.

4.2. Method (T3)

To address the suspected difficulties that the patient had in discerning the local level of the stimuli in T2, in T3 we first adjusted the size and other parameters of the visual stimuli so that the patient was able to discriminate its local features. We used the method of adjustment to establish the size of the stimuli. A single Navon stimulus (2.88° x 4.82°) was displayed ±2.18° to one side of the central fixation cross and remained on the screen until the patient's response. We gradually increased the size (0.5° increments in each dimension) and the distance from the fixation cross (in 0.3° increments) across consecutive blocks until the patient reported that she could easily discriminate the small letters and identify them correctly in both visual fields. In the final Global-Local Processing task, we used stimuli that were 5.13° x 7.10° at the global level (local level 0.92° x 1.26°) presented at a distance of ±3.38° between the fixation cross and the centre of the stimulus.

4.3. Results (T3)

In addition to the results reported in the main article, we also examined whether any of the differences in global precedence, local interference, and global interference effects were limited to processing of visual stimuli that appear in the affected side of space (LVF) or could be observed for visual stimuli on both sides of space (LVF and RVF). Visual field comparisons between the patient and controls through RSDTs showed that the patient had larger global precedence in reaction times in the LVF than the RVF, $t(11) = 9.41$, $p < .001$, $z_{cc} = 12.026$, 95% CI [5.268, 20.358], compared to controls. We also found larger local interference in the RVF than the LVF for accuracy rates, $t(11) = 3.32$, $p = .007$, $z_{cc} = 3.643$, 95% CI [-0.978, 8.998], and larger local interference in the LVF than the RVF for reaction times, $t(11) = 28.31$, $p < .001$, $z_{cc} = 72.960$, 95% CI [28.462, 124.837]. The patient's global interference effects for reaction times were also larger in the LVF than the RVF, $t(11) = 19.08$, $p < .001$, $z_{cc} = 35.770$, 95% CI [-14.903, 90.740]. Overall, there was no systematic pattern linking the patient's global / local processing biases to the affected side of space. Although some effects appear to be stronger in the LVF (affected side), consistent biases were present in both visual fields.

5. Rarebit perimetry (Frisén, 2002)

5.1. Method

The test was conducted in a darkened room, one eye at the time. An eye-patch was used to cover the eye that was not being tested. The participants were required to follow the fixation cross and detect minute stimuli (rare bits) presented at different locations on a black screen, across a visual field that extended ±20° vertically and ±30° horizontally. They used one key press to indicate that they detected one stimulus and two key presses if they detected two stimuli in each trial. The participants completed a demonstration session that was followed by five blocks of trials testing inner zone of the visual field at 100cm viewing distance. Then they completed five more blocks of trials testing outer zone at 50cm viewing distance.

6. Landolt C

6.1. Method

We developed the Landolt C task to map the participants' binocular peripheral visual acuity in the manner resembling the presentation of other experimental tasks assessing visual spatial attention in this study. We used Landolt C optotypes presented as rings with a gap on the top, bottom, left, or right side. To establish the size of the stimuli that the patient was able to discriminate at 50cm viewing distance, we first presented the optotypes ±3° from the central 0.46° x 0.46° fixation cross. The size of the stimuli varied from 0.5° x 0.5° to 3° x 3° in 0.5° increments. Stimuli were displayed for 500ms, with 500ms inter-trial intervals. The patient reported the orientation of the gap in Landolt C optotypes. After completing 48 trials (each orientation presented once on both sides of the screen in six different sizes, 4 x 2 x 6), we chose the size 1° larger than the smallest size for which the patient's accuracy was 100% at ±3º from central vision (size 2° x 2°).

In each trial, the participants focused of a central fixation cross, which after 500ms was joined by an optotype in one of the four orientations. The optotypes were presented for 200ms to the left or to the right of the fixation cross at one of six distances (± 3°, 5°, 8°, 12°, 17°, 23°) on the horizontal plane. The participants indicated the orientation of the gap in Landolt C in each trial by pressing "up", "down", "left", or "right" arrow keys on the keyboard with their right hand, without time constraint. There were 144 pseudo-randomised trials, i.e., each orientation was presented 3 times in each position relative to the fixation cross (4 x 3 x 12). We analysed the percentages of correct responses given by the patient vs controls for each position relative to the fixation cross.

Table S1 *The patient's and controls' mean (±SD) PSS values in each Response condition, and PSS values averaged across two Response conditions in each Presentation condition of the Temporal Order Judgement tasks*

Time point	Presentation condition	Response condition				Averaged PSS	
		"Which side occurred first?"		"Which side occurred second?"			
		Patient	Controls	Patient	Controls	Patient	Controls
T1[a]	Crossed Hands (visual)	-[b]	-6.6±33.9	-	-	-[b]	-6.6±33.9
	Uncrossed Hands (visual)	-83.7±49.65[c]	-4.9±20.1	-	-	-83.7±49.65[c]	-4.9±20.1
	Board (visual)	-42.22±58.66	-2.9±33.4	-	-	-42.22±58.66	-2.9±33.4
T2	Crossed Hands (visual)	-207.42±330.85	12.86±29.84	-	19.18±26.94	-	16.02±26.3
	Uncrossed Hands (visual)	-19.89±76.29	12.21±17.64	-84.07±77.27	-3.76±26.58	-51.98±76.78	4.23±18.23
	Board (visual)	-82.92±128.5	4.11±28.9	13.08±73.11	12.21±17.64	-34.92±100.81	2.3±18.19
T3	Board (visual)	16.26±41.25	-3.76±20.9	42.45±42.86	-6.71±13.24	29.36±42.06	-5.23±10.95
	Wall (visual)	44.97±25.24	3.22±18.69	40.15±32.99	1.17±16.92	42.56±29.11	2.2±13.71
	Knees (tactile)	68.94±62.55	-1.77±31.65	98.48±56.38	2.76±15.76	83.71±59.47	0.49±18.11

Note. T1 = Session 1; T2 = Session 2; T3 = Session3. SDs were calculated within-subject for the patient, and between-subjects for the controls.

[a] The TOJ tasks in T1 were conducted only in one Response condition ("which side occurred first"). [b] Lack of systematic pattern of the patient's responses across different temporal offsets in Crossed Hands conditions ("which side occurred first" in T1 and "which side occurred second" in T2) prevented fitting the cumulative Gaussian to determine PSSs, therefore only controls' results are presented for these conditions. [c] Due to 95% "right" response in Uncrossed Hands condition in T1, nearest neighbour replacement was used to give a conservative estimate of the patient's PSS from other patient responses.

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Chapter 3 – Additional Files

Pain Reduction by Inducing Sensory-Motor Adaptation in Complex Regional Pain Syndrome (CRPS PRISMA): Protocol for a Double-blind Randomized Controlled Trial

Additional file 1 - World Health Organization Trial Registration Data Set

Table S1 *WHO Trial Registration Data Set*

Data category	**Information**
Primary registry and trial identifying number	International Standard Randomised Controlled Trial Number ISRCTN46828292
Date of registration in primary registry	27/03/2017
Secondary identifying numbers	Oxford A REC 12/sc/0667, University of Bath Psychology Ethics Committee 16-333
Source(s) of monetary or material support	Reflex Sympathetic Dystrophy Syndrome Association (USA)
Primary sponsor	University of Bath (UK)
Secondary sponsor(s)	NA
Contact for public queries	Ms Monika Halicka (m.halicka@bath.ac.uk), Dr Janet Bultitude (j.bultitude@bath.ac.uk)
Contact for scientific queries	Ms Monika Halicka (m.halicka@bath.ac.uk), Dr Janet Bultitude (j.bultitude@bath.ac.uk)
Public title	Treatment of complex regional pain syndrome (CRPS) with sensory-motor adaptation
Scientific title	Pain Reduction by Inducing Sensory-Motor Adaptation in Complex Regional Pain Syndrome (CRPS PRISMA): Protocol for a Double-blind Randomized Controlled Trial
Countries of recruitment	United Kingdom
Health condition(s) or problem(s) studied	Complex Regional Pain Syndrome
Intervention(s)	Active comparator: Prism Adaptation Treatment (two weeks of twice-daily sensory-motor training using 35-diopter Fresnel lenses that induce visual shift away from the CRPS-affected side)
	Placebo comparator: Sham Prism Adaptation (Sham Treatment) (the same procedure using neutral lenses that do not induce visual shift)
Key inclusion and exclusion criteria	Inclusion criteria (Participants with CRPS): male/female; age 18-80; CRPS type I primarily affecting one upper limb, meeting Budapest diagnostic research criteria , for >3 months; current pain intensity min. 2/10
	Exclusion criteria (Participants with CRPS): insufficient English language ability; legally blind; CRPS affecting both sides of the body; CRPS II (confirmed nerve

Data category	Information
	damage); physical limitation preventing execution of Prism Adaptation / sham treatment; severe psychiatric comorbidity
	Inclusion criteria (Healthy control participants): male/female; age 18-80; neurologically healthy; no current or chronic pain
	Exclusion criteria (Healthy control participants): insufficient English language ability; legally blind; physical disability or injury limiting normal mobility; history of neurological or severe psychiatric illness
Study type	Interventional
	Allocation: Randomized (with stratification to minimise baseline group differences) Blinding: Double-blind (Participants with CRPS, outcomes assessor) Assignment: Parallel
	Primary purpose: treatment
Date of first enrolment	19/06/2017
Target sample size	42 Participants with CRPS, 21 Healthy control participants
Recruitment status	No longer recruiting
Primary outcome(s)	Current self-reported pain intensity on a 0 (no pain) to 10 (pain as bad as you can imagine) Numerical Rating Scale CRPS severity score based on 16-points scoring system by Harden et al. (*PAIN*, 2017) Time points: Immediately before the commencement of treatment (week 4) vs. immediately after the end of the treatment period (week 7)
Key secondary outcomes	Self-report questionnaires about pain, physical and emotional functioning, body representation, expectations about treatment, and impressions of treatment outcome in weeks 1, 4, 7, 11, 19, and 31 (Brief Pain Inventory – short form, Pain Detect Questionnaire, Bath CRPS Body Perception Disturbance Scale, Tampa Scale for Kinesiophobia, Profile of Mood States); week 1 (Edinburgh Handedness Inventory, Revised Life Orientation Test, Patient-Centred Outcomes Questionnaire); and weeks 7, 11, 19, and 31 (Patient Global Impression of Change) Self-reported daily ratings of average pain intensity, range of movement, and the extent to which the CRPS symptoms interfere with daily life (weeks 1 to 11) Clinical assessments of CRPS signs and symptoms and sensory, motor, and autonomic function in weeks 1, 4, 7, and 11 (CRPS severity score, limb temperature asymmetry, oedema, grip strength, delta finger-to-palm distance, mechanical detection threshold, mechanical pain threshold, mechanical allodynia, two-point discrimination threshold) Computer-based tests of visuospatial attention (Temporal Order Judgement, Landmark, and Greyscales tasks), cognitive representation of space (Mental Number Line Bisection task), spatially-defined motor function (Directional Hypokinesia task), and body representation (Hand Laterality Recognition task) in weeks 1, 4, 7, and 11

Additional file 2 - Supplementary text describing the procedure and results of a pilot study to select the stimulus set for the Hand Laterality Recognition task

To develop a stimulus set for the Hand Laterality Recognition task, we photographed a gender-neutral right hand in 36 different postures and mirror-reversed the images to create equivalent pictures of a left hand. In a pilot study, these images were presented at four different orientations (0°, 90°, 180° and 270°), each in left and right visual field (giving a total of 576 trials). In each trail, a black 0.1° fixation cross on a white background was on constant display. After 1000ms a colour image of a hand (12° x 12°) was randomly presented 8° to the left or to the right of the fixation cross (i.e., in the left or the right visual field) for 200ms. The pilot participants (N = 22 healthy adults; 11 females; mean age = 27.91; SD = 8.43) were required to indicate whether the image represented the right or the left hand by pressing "up" or "down" keys, respectively, using the index and middle fingers of their dominant hand. The next trial started after 3000ms from the stimulus onset or once the response was given, whichever came first. Participants were instructed to be as fast and as accurate in their responses as possible. Following a practice session with longer stimulus presentation times (2000ms), participants completed the task in three blocks, allowing a break after every 196 trials. Fifty images (25 of each hand in the same posture and orientation) were selected from the pilot image bank for the current study based on sufficient accuracy obtained in the pilot study: at least 72% accuracy averaged across both hemifields and less than 15% difference in accuracy between left and right hemifield. These requirements were set to ensure that the stimuli properties were such that a healthy participant is able to determine the laterality above the chance level. Example stimuli are presented in Figure 6 in the manuscript.

Additional file 3 - SPIRIT 2013 Checklist

Table S2 *Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	131
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	132
	2b	All items from the World Health Organization Trial Registration Data Set	Additional file 1
Protocol version	3	Date and version identifier	132
Funding	4	Sources and types of financial, material, and other support	139, 168
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	131, 168
	5b	Name and contact information for the trial sponsor	167
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	167
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	139-142, 159, 167-168
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	133-135, 142
	6b	Explanation for choice of comparators	134, 141
Objectives	7	Specific objectives or hypotheses	134-135
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	133-135, 140
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	137
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	137-139

Section/item	Item No	Description	Addressed on page number
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	140-1342
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	136, 142
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	141-142
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	142
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	133-159, Table 3
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	135-137, Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	160-161
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	139
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	140, Table 2
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	140
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	140
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	135, 159-160
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	159
Methods: Data collection, management, and analysis			

Section/item	Item No	Description	Addressed on page number
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	143-159, 168
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	139, 161-162
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	146-159, 168
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	161-165
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	161-165
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	161-162
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	161
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	162
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	167
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	167
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	167-168

Section/item	Item No	Description	Addressed on page number
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	168
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	168
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	168
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	139
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	168
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	168
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

Chapter 4 - Supplementary Material

Disputing space-based biases in unilateral complex regional pain syndrome

1. Spatially-defined motor function - results

The results of the linear mixed models analyses on the spatially-defined motor function task data are reported in Table S1. In the main text, we reported the main effects of Group on movement initiation times with either hand, indicating that participants with Complex Regional Syndrome (CRPS) were overall slower compared to controls. There was also a main effect of Starting Position on initiation times with the affected limb suggesting that, regardless of Group or Visual Field (VF), movement initiation was slower from the affected (*Mdn* = 477.32, BCa 95% CI [455.98, 532.44]) than unaffected side of space (*Mdn* = 458.88, BCa 95% CI [435.17, 505.13]). This pattern is consistent with directional hypokinesia towards the unaffected side (i.e. slowing of movements directed toward the unaffected, rather than affected side of space).

Also reported in the main text is that main effects of Group were also found for movement execution times with either hand, with slowing among CRPS patients relative to controls. There was also an interaction between Group and hand Starting Position for the unaffected limb, suggesting slower execution of movements from the unaffected than affected Starting Position among CRPS patients compared to controls. In addition to these results reported in the main text, we found the following effects on execution times that did not involve Group.

A main effect of VF suggested that, independent of Group or Starting Position, execution of movements with the affected limb was slower towards the targets in the unaffected (*Mdn* = 891.65, BCa 95% CI [795.69, 939.31]) compared to the affected (*Mdn* = 826.69, BCa 95% CI [770.99, 924.28]) side of space. This suggests that movements to the targets in the side of space ipsilateral to the affected limb were faster than to the contralateral side of space.

Main effects of Starting Position also indicated overall slower movement execution from the affected (*Mdn* = 937.65, BCa 95% CI [810.78, 980.04]) than central (*Mdn* 799.22, BCa 95% CI [743.69, 880.67]) position with the affected limb, and from the unaffected (*Mdn* = 786.88, BCa 95% CI [739.55, 847.88]) than affected (*Mdn* = 750.09, BCa 95% CI [707.51, 803.14]) position with the unaffected limb, regardless of Group or VF. These suggest that movements from starting positions ipsilateral to the hand used were slower than from contralateral or central positions.

Furthermore, there were interactions between Starting Position and VF on execution times. When executing movements with the affected or unaffected hand, participants were slower in reaching targets in the unaffected VF (affected hand *Mdn* = 943.60, BCa 95% CI [847.43, 1047.72]; unaffected hand *Mdn* = 789.42, BCa 95% CI [702.34, 824.93]) than affected VF (affected hand *Mdn* = 887.55, BCa 95% CI [790.22, 926.11]; unaffected hand *Mdn* = 726.93, BCa 95% CI

[681.03, 774.97]) from the affected Starting Position (Figure S1a). Conversely, from the unaffected Starting Position, participants were slower in reaching targets in the affected VF (affected hand *Mdn* = 857.01, BCa 95% CI [781.54, 931.30]; unaffected hand *Mdn* = 821.87, BCa 95% CI [776.09, 860.07]) than unaffected VF (affected hand *Mdn* = 814.83, BCa 95% CI [754.59, 905.28]; unaffected hand *Mdn* = 759.12, BCa 95% CI [705.55, 802.46]) (Figure S1b). Movement execution with the affected hand towards the targets in the unaffected VF was significantly slower from the affected than unaffected Starting Position (Figure S1c), whereas when the unaffected hand was used, movement execution to the targets in the affected VF was significantly slower from the unaffected than affected Starting Position (Figure S1d). These interactions suggest that regardless of Group, participants were slower to execute the longer movements that crossed the body midline with either hand than to execute the shorter movements that were made within the same side of the body midline. Additionally, participants were slower to execute movements from the central Starting Position with the unaffected hand towards the affected VF (*Mdn* = 717.05, BCa 95% CI [679.23, 802.12]) than unaffected VF (*Mdn* = 690.13, BCa 95% CI [637.05, 754.59]), regardless of Group (Figure S1e). This effect would be consistent with directional bradykinesia towards the affected side. Alternatively, it could reflect slowing of movement to the side of space contralateral to the limb used. However, execution of the unaffected hand movements towards the unaffected VF (that is, side of space ipsilateral to the limb used) was also slower from the affected than central Starting Position (Figure S1f). There were no further significant main effects or interactions for movement execution times.

Overall, the results provide some evidence for directional bradykinesia towards the affected side when using the unaffected limb, as well as directional hypokinesia and bradykinesia towards the unaffected side when using the affected limb. However, these patterns were not specific to CRPS, but largely consistent across both groups. Most of the significant effects for movement execution time as a function of hand starting position and target location can be explained by the length of the required movement pathway and whether it crossed the body midline. In summary, we observed little systematic evidence of directional motor deficits consistent with motor neglect in participants with CRPS.

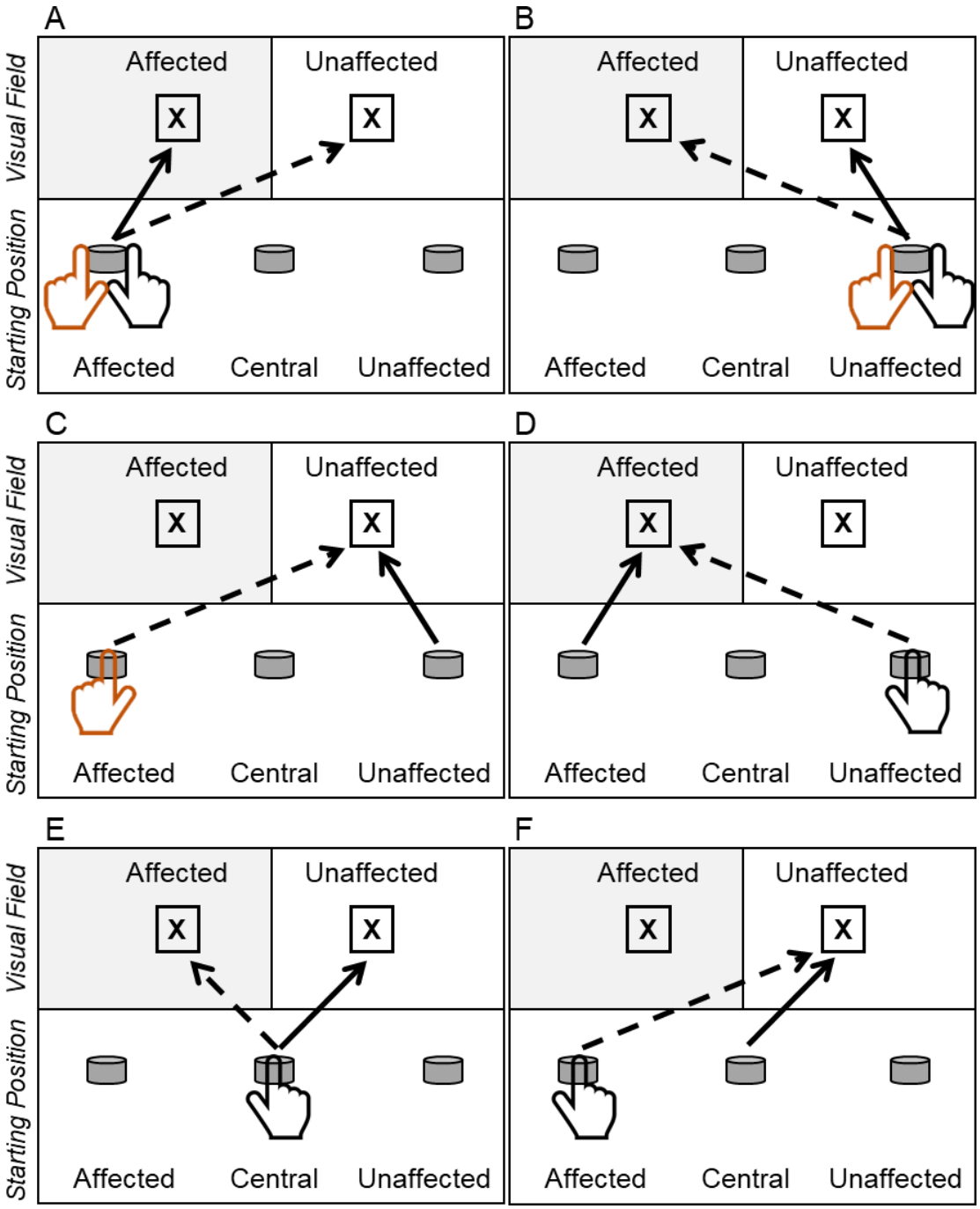

Figure S1. Diagrams illustrate the results of significant post-hoc contrasts following Starting Position x Visual Field interactions on movement execution times with the affected (orange) and unaffected (black) hand. Arrows indicate the direction of movement. Dashed lines represent slower movement execution as compared to solid lines. "X" represents the target, and the grey cylinders represent the possible button locations / hand Starting Positions. Regardless of Group, participants were slower to execute movements (A) towards the unaffected VF than affected VF from the affected Starting Position, with either hand; (B) towards the unaffected VF than affected VF from the unaffected Starting Position, with either hand; (C) towards the unaffected VF from the affected than unaffected Starting Position, with the affected hand; (D) towards the affected VF from the unaffected than affected Starting Position, with the unaffected hand; (E) towards the affected VF than unaffected VF from the central Starting Position, with the unaffected hand; (F) towards the unaffected VF from the affected than central Starting Position, with the unaffected hand.

Table S1 *The results of bootstrapped (n = 1000) linear mixed modelling of main effects and interactions on movement initiation / execution times for each hand in the test of spatially-defined motor function*

Model term	Movement initiation time Affected hand			Movement initiation time Unaffected hand			Movement execution time Affected hand			Movement execution time Unaffected hand		
	Regression coefficient	Lower 95% CI	Upper 95% CI	Regression coefficient	Lower 95% CI	Upper 95% CI	Regression coefficient	Lower 95% CI	Upper 95% CI	Regression coefficient	Lower 95% CI	Upper 95% CI
Intercept	0.433*	0.425	0.440	0.421*	0.413	0.429	0.693*	0.674	0.713	0.672*	0.641	0.702
Group (Con vs CRPS)	0.191*	0.159	0.222	0.073*	0.049	0.099	0.444*	0.357	0.523	0.112*	0.077	0.147
Starting Position (AP vs CP)	-0.009	-0.021	0.003	0.006	-0.005	0.019	-0.083*	-0.112	-0.057	0.006	-0.040	0.054
Starting Position (AP vs UP)	-0.025*	-0.036	-0.012	0.006	-0.008	0.020	-0.006	-0.044	0.029	0.066*	0.015	0.118
Visual Field (AVF vs UVF)	-0.005	-0.016	0.007	-0.007	-0.019	0.004	0.050*	0.021	0.078	0.021	-0.021	0.061
Group (Con vs CRPS) x Starting Position (AP vs CP)	-0.008	-0.049	0.038	-0.020	-0.055	0.008	-0.010	-0.109	0.085	0.007	-0.044	0.061
Group (Con vs CRPS) x Starting Position (AP vs UP)	0.010	-0.035	0.055	-0.008	-0.043	0.023	0.047	-0.064	0.164	0.063*	0.002	0.120
Group (Con vs CRPS) x Visual Field (AVF vs UVF)	0.023	-0.021	0.068	-0.010	-0.041	0.018	0.110	-0.003	0.222	0.020	-0.029	0.068
Starting Position (AP vs CP) x Visual Field (AVF vs UVF)	0.008	-0.010	0.024	0.004	-0.013	0.022	-0.023	-0.057	0.012	-0.066*	-0.126	< -0.001
Starting Position (AP vs UP) x Visual Field (AVF vs UVF)	0.009	-0.008	0.026	0.006	-0.012	0.025	-0.085*	-0.129	-0.040	-0.079*	-0.143	-0.014
Group (Con vs CRPS) x Starting Position (AP vs CP) x Visual Field (AVF vs UVF)	-0.005	-0.062	0.052	-0.004	-0.041	0.037	0.060	-0.123	0.284	-0.022	-0.099	0.052
Group (Con vs CRPS) x Starting Position (AP vs UP) x Visual Field (AVF vs UVF)	-0.005	-0.077	0.068	0.011	-0.025	0.050	-0.105	-0.264	0.051	-0.036	-0.109	0.042

Note. *Significant effect (95% CI around the regression coefficient estimate does not include zero). The levels of each model term are indicated in brackets, with the reference term listed first. Group factor had two levels (Con = control participants, CRPS = participants with Complex Regional Pain Syndrome) and Visual Field factor also had two levels (AVF = affected, UVF = unaffected). The hand Starting Position factor had three levels (CP = central, AP = affected, UP = unaffected), necessitating the inclusion of two terms in the model for each main effect and interaction involving this Factor.

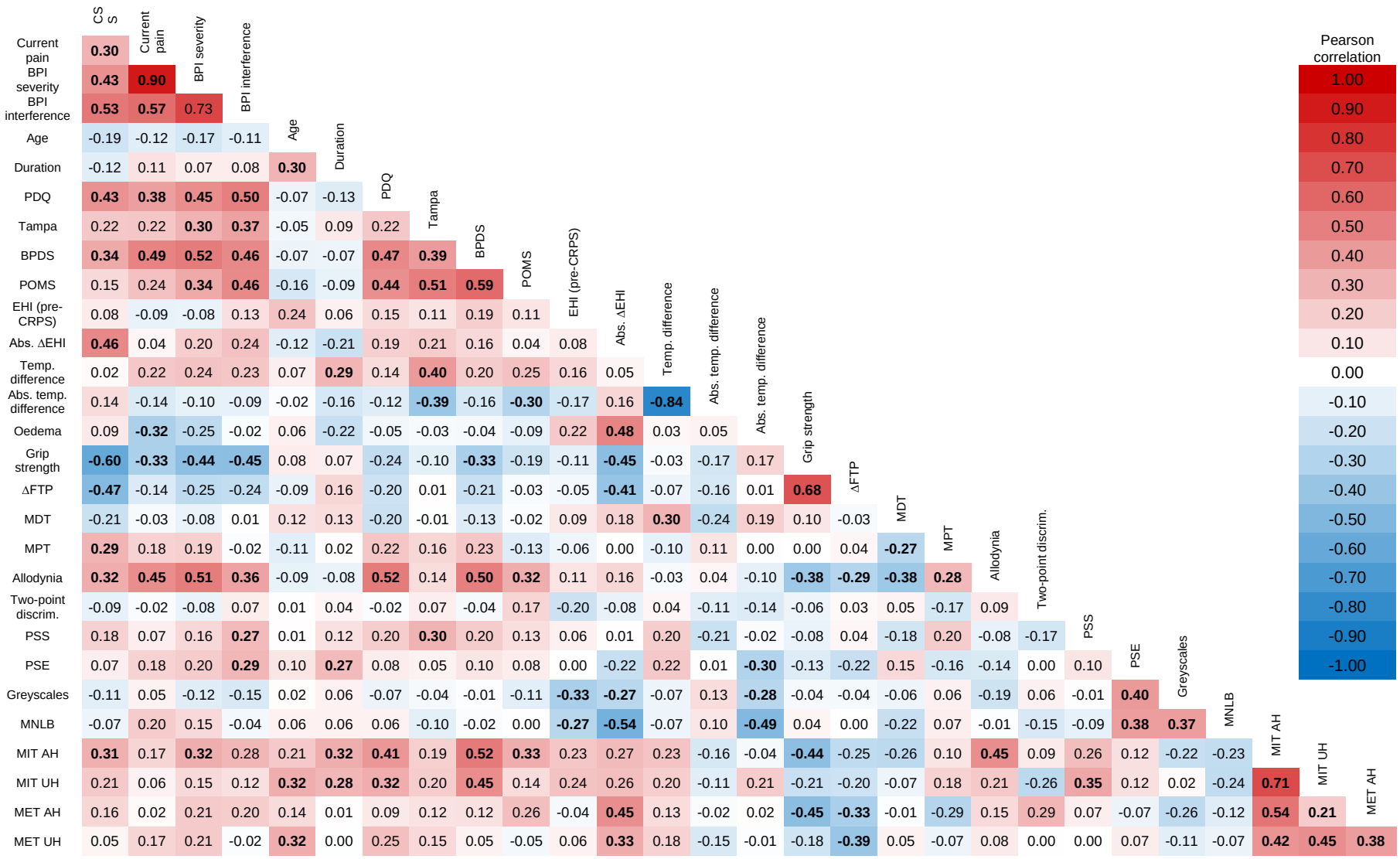
CSS
Current pain
BPI severity
BPI interference
Age
Duration
PDQ
Tampa
BPDS
POMS
EHI (pre-CRPS)
Abs. ΔEHI
Temp. difference
Abs. temp. difference
Abs. temp. difference
Grip strength
ΔFTP
MDT
MPT
Allodynia
Two-point discrim.
PSS
PSE
Greyscales
MNLB
MIT AH
MIT UH
MET AH
Current pain 0.30
BPI severity 0.43 0.90
BPI interference 0.53 0.57 0.73
Age -0.19 -0.12 -0.17 -0.11
Duration -0.12 0.11 0.07 0.08 0.30
PDQ 0.43 0.38 0.45 0.50 -0.07 -0.13
Tampa 0.22 0.22 0.30 0.37 -0.05 0.09 0.22
BPDS 0.34 0.49 0.52 0.46 -0.07 -0.07 0.47 0.39
POMS 0.15 0.24 0.34 0.46 -0.16 -0.09 0.44 0.51 0.59
EHI (pre-CRPS) 0.08 -0.09 -0.08 0.13 0.24 0.06 0.15 0.11 0.19 0.11
Abs. ΔEHI 0.46 0.04 0.20 0.24 -0.12 -0.21 0.19 0.21 0.16 0.04 0.08
Temp. difference 0.02 0.22 0.24 0.23 0.07 0.29 0.14 0.40 0.20 0.25 0.16 0.05
Abs. temp. difference 0.14 -0.14 -0.10 -0.09 -0.02 -0.16 -0.12 -0.39 -0.16 -0.30 -0.17 0.16 -0.84
Oedema 0.09 -0.32 -0.25 -0.02 0.06 -0.22 -0.05 -0.03 -0.04 -0.09 0.22 0.48 0.03 0.05
Grip strength -0.60 -0.33 -0.44 -0.45 0.08 0.07 -0.24 -0.10 -0.33 -0.19 -0.11 -0.45 -0.03 -0.17 0.17
ΔFTP -0.47 -0.14 -0.25 -0.24 -0.09 0.16 -0.20 0.01 -0.21 -0.03 -0.05 -0.41 -0.07 -0.16 0.01 0.68
MDT -0.21 -0.03 -0.08 0.01 0.12 0.13 -0.20 -0.01 -0.13 -0.02 0.09 0.18 0.30 -0.24 0.19 0.10 -0.03
MPT 0.29 0.18 0.19 -0.02 -0.11 0.02 0.22 0.16 0.23 -0.13 -0.06 0.00 -0.10 0.11 0.00 0.00 0.04 -0.27
Allodynia 0.32 0.45 0.51 0.36 -0.09 -0.08 0.52 0.14 0.50 0.32 0.11 0.16 -0.03 0.04 -0.10 -0.38 -0.29 -0.38 0.28
Two-point discrim. -0.09 -0.02 -0.08 0.07 0.01 0.04 -0.02 0.07 -0.04 0.17 -0.20 -0.08 0.04 -0.11 -0.14 -0.06 0.03 0.05 -0.17 0.09
PSS 0.18 0.07 0.16 0.27 0.01 0.12 0.20 0.30 0.20 0.13 0.06 0.01 0.20 -0.21 -0.02 -0.08 0.04 -0.18 0.20 -0.08 -0.17
PSE 0.07 0.18 0.20 0.29 0.10 0.27 0.08 0.05 0.10 0.08 0.00 -0.22 0.22 0.01 -0.30 -0.13 -0.22 0.15 -0.16 -0.14 0.00 0.10
Greyscales -0.11 0.05 -0.12 -0.15 0.02 0.06 -0.07 -0.04 -0.01 -0.11 -0.33 -0.27 -0.07 0.13 -0.28 -0.04 -0.04 -0.06 0.06 -0.19 0.06 -0.01 0.40
MNLB -0.07 0.20 0.15 -0.04 0.06 0.06 0.06 -0.10 -0.02 0.00 -0.27 -0.54 -0.07 0.10 -0.49 0.04 0.00 -0.22 0.07 -0.01 -0.15 -0.09 0.38 0.37
MIT AH 0.31 0.17 0.32 0.28 0.21 0.32 0.41 0.19 0.52 0.33 0.23 0.27 0.23 -0.16 -0.04 -0.44 -0.25 -0.26 0.10 0.45 0.09 0.26 0.12 -0.22 -0.23
MIT UH 0.21 0.06 0.15 0.12 0.32 0.28 0.32 0.20 0.45 0.14 0.24 0.26 0.20 -0.11 0.21 -0.21 -0.20 -0.07 0.18 0.21 -0.26 0.35 0.12 0.02 -0.24 0.71
MET AH 0.16 0.02 0.21 0.20 0.14 0.01 0.09 0.12 0.12 0.26 -0.04 0.45 0.13 -0.02 0.02 -0.45 -0.33 -0.01 -0.29 0.15 0.29 0.07 -0.07 -0.26 -0.12 0.54 0.21
MET UH 0.05 0.17 0.21 -0.02 0.32 0.00 0.25 0.15 0.05 -0.05 0.06 0.33 0.18 -0.15 -0.01 -0.18 -0.39 0.05 -0.07 0.08 0.00 0.00 0.07 -0.11 -0.07 0.42 0.45 0.38
Pearson correlation
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
-0.20
-0.30
-0.40
-0.50
-0.60
-0.70
-0.80
-0.90
-1.00

Figure S2. Correlation matrix illustrating relationships between participant characteristics; self-reported pain, fear of movement, body perception, and mood; sensory, motor, and autonomic function; and experimental measures of visuospatial attention, mental representation of space, and movement speed. The numbers represent the Pearson's correlation coefficient. The strength and direction of the correlations are colour-coded according to the legend on the right-hand side. Numbers in bold represent correlations significant at the level of $p < .05$. CSS = CRPS symptom severity score; BPI = Brief Pain Inventory; PDQ = Pain Detect Questionnaire; Tampa = Tampa Scale for Kinesiophobia; BPDS = Bath CRPS Body Perception Disturbance Scale; POMS = Profile of Mood States; EHI = Edinburgh Handedness Inventory; Abs. ΔEHI = absolute change in handedness index from before CRPS onset to current handedness; ΔFTP = Finger-To-Palm distance; MDT = Mechanical Detection Threshold; MPT = Mechanical Pain Threshold; PSS = Point of Subjective Simultaneity; PSE = Point of Subjective Equality; MNLB = Mental Number Line Bisection; MIT AH = movement initiation time with the affected hand; MIT UH = movement initiation time with the unaffected hand; MET AH = movement execution time with the affected hand; MET UH = movement execution time with the unaffected hand.

Chapter 5 - Supplemental Material

Supplemental text

Text S1. Summary of any deviations from the original trial protocol

Deviations from the protocol [3] (Chapter 3):

1. Universities of Oxford and Exeter were listed as research sites in the trial protocol, however, no participants were tested in these locations.
2. In the original protocol, we defined intention-to-treat population as all participants allocated to treatment, regardless of their adherence or completion of outcome measures. This did not account for the possibility that participants could drop out after treatment allocation but before they received the treatment, that is, before they were trained in how to carry out their allocated intervention. For instance, this was the case when participant was allocated to treatment but did not show up for RS2 and did not cancel their appointment beforehand. Therefore, in this manuscript we defined the intention-to-treat population as those participants who received their allocated treatment (i.e. received in-person training) immediately after RS2.
3. The treatment protocol stated that the targets will be located at approximately 60cm distance from the participant. In the manuscript we reported the actual measured distance, on average 50cm, which depended on how far participant could extend their arm.
4. We stated that we will report the total number of treatment sessions per group in which deviations other than missed or extra sessions were suspected, however, no such deviations were identified.
5. Although the protocol stated that we will calculate the Number Needed to Treat for the primary outcomes, we did not perform these analyses because there was no effect of prism adaptation (PA) treatment. Nonetheless, we reported effects sizes for mean between-group differences in change on the primary outcomes over the treatment period, which was not explicitly included in the protocol.
6. The protocol mentioned that we would take thermal images of participants' arms when available, however, we only had access to a thermal imaging camera when testing the first few participants, thus we did not include the images or performed any formal analyses for this manuscript.
7. It was not specified in the protocol whether we would analyse signed or absolute limb temperature difference. For this manuscript, we conducted analyses on the absolute temperature difference, to test whether PA treatment can reduce temperature asymmetry, regardless of whether the affected limb was colder or warmer than unaffected limb at baseline.
8. In the protocol we stated that we would conduct exploratory analyses of potential predictors of response to PA treatment and/or CRPS progression over time. We only explored the factors that could account for the second outcome, because we did not find any effects of PA

treatment beyond that of sham treatment. Furthermore, we used pain intensity ratings across six rather than four time points (i.e. including the long-term follow-up), to capture change in pain over longer period. Moreover, we stated in the protocol that in the first instance we would consider those factors on which participants with CRPS significantly differed from pain-free participants at baseline, to be potential predictors in the regression models. However, participants with CRPS did not present with hypothesised abnormalities on the tests of neuropsychological functions compared to controls [2] (Chapter 4). Thus, we included all primary and secondary outcomes in best subsets regression analyses to allow unbiased selection of the best combination of explanatory variables. These analyses were explicitly identified as exploratory both in the original protocol, and in this manuscript.

9. Exploratory subgroup analyses were not specified in the protocol but were clearly labelled as such in the manuscript and supplementary files. These were conducted to aid interpretation of our findings that PA did not affect participants' pain intensity, CRPS severity, or spatial cognition, as we initially hypothesised.

Text S2. Instructions for training CRPS participants in therapy for PRISMA trial (script)

"I'm going to read the instructions out to you. This makes sure that I don't forget anything, and also that everyone hears the same instructions. Feel free to ask me any questions if anything is unclear".

"I am going to train you in how to perform sensorimotor adaptation therapy. You will perform the therapy twice a day, and each time it should take no more than a few minutes. The therapy involves making some pointing movements while wearing some goggles that distort your vision. I am going to explain the entire process to you now, and we will go through the first therapy session together. After today, you can refer to these written instructions to help you remember how to perform the therapy. We have also included a link to a video that shows the entire therapy"

Point out the video link in the instructions.

*"*We will watch this now together and then I will go through the entire therapy with you."

Show participant the training video. Write in pen and in large letters under the link to the video which arm they should use for the treatment (it should be their affected arm). If their affected arm is their left arm then make a point of saying that they will do everything the same as in the video, except that they will use their LEFT arm (not the right, as shown in the video).

"First we need to put this sheet up on the wall. This needs to be placed so that the red circles are at the same level as your eyes, and this black arrow is in line with the centre of your body. You should be able to reach both of the circles with your affected arm stretched out almost as far as it can go."

If you are meeting them in their own home, fix the sheet in the place where they will do their treatment sessions. Have the participant do this themselves if possible, and help them and/or correct them if necessary.

Have the participant position their chair in front of the pointing sheet and reach to touch each of the targets. Have them move their chair closer/further away if necessary. They should be able to reach the targets with their arm slightly less than fully outstretched. ***Measure and record the distance between their eyes and the centre of the page upon which the targets are printed.***

"You're going to make pointing movements to each of these dots. You need to start with your finger on your chest, then reach out and touch the left target, then bring your hand immediately back to your chest, then reach out and touch the right target, and so on". *(perform these movements yourself while you talk).* "I want you to do this as fast as possible" (*demonstrate*).

They should use their index finger to point if possible, otherwise they can use whichever finger is most comfortable, but is MUST be a finger of their affected hand. They can also point with a knuckle. ***Make note of any such adjustments.***

"Before we start the treatment, I'll have you practice the pointing movements.

Have the participant practice these movements. Correct them if necessary.

"That was just a practice to make sure you have the hang of the movements that are required during treatment. During the treatment, you will put your goggles on and make these movements as fast as possible a total of 50 times. That's 25 times per dot"

Take the goggles out of the bag. Fiddle with the lenses a little as though you are adjusting them, and then look through them as though you are checking that they are correct.

"These goggles distort your vision in a few different ways. For example, they restrict your field of vision, and they also make your vision a bit foggy. They will make it a bit more difficult to point to the targets. The treatment that we are testing seems to work by forcing the brain to re-learn how to combine different sources of information about where your limb is while it moves."

"Because the goggles distort your vision, you might be tempted to slow down your pointing movements. It is VERY important that you resist the temptation to slow down. Even if you miss the targets at first, keep moving and you will find that after a few goes you will probably become more accurate again."

"Once you have put the goggles on, it is important that you move your head as little as possible, however you should make sure that you can see both of the red dots. You will need to count your pointing movements and stop when you reach fifty. Do you have any questions?"

Answer any questions that the participant has (within reason!). Once they are happy to start the treatment, give them the goggles and let them do the treatment. Ask them to count their own pointing movements aloud. Let them run the treatment themselves as much as possible, but provide advice and feedback if necessary. This could include urging them to move rapidly if you see them slowing down in order to hit the target, reminding them to bring their hand all the way back to their chest in between pointing movements, or making sure that they stop after 50 pointing

movements. If participants find it hard to make high-quality pointing movements for 50 trials in a row, have them stop to rest after 25. If this is necessary, then have them close their eyes while they are resting, and tell them to use the same procedure for all of their treatment sessions. **Make a note of this in your own records and also in their instruction sheet or log book.**

Once the participant has finished have them take the goggles off.

"The treatment that you will do from now on will be exactly the same as what you just did while wearing the goggles. You don't need to do any of the pointing that we did before you put the goggles on, just the 50 pointing movements while wearing goggles. You will do this twice a day. You should aim to do the two treatment sessions about 12 hours apart from each other, although we advise that you just find a way to make it part of your normal morning and evening routine, even if this means that the treatments aren't exactly 12 hours apart. I'd like you to decide now when you will do the treatments"

Ask them to choose 2 times of day that are roughly 12 hours apart, and ***write these times in their log book.*** *Talk the participant through the logbook. The notes section is where they could write any information they think is relevant, e.g. anything that might have meant the treatment session proceeded differently (e.g. it was completed late due to coming home last), or reasons for missed sessions.*

"It's very important that you do all of the treatment sessions, regardless of whether your symptoms improve or stay the same. One thing that we do know about this treatment is that any benefits seem only to arise after several days of treatment, and the number of days is likely to vary between people. So even if you're in the real treatment group, it might take a few days for you to feel any changes in symptoms. Even if you don't think your symptoms are changing, please complete all of the treatment sessions. It might be that you are in the real treatment group but that your symptoms aren't relieved by the treatment, in which case it would be very important for us to know that you have done the full two weeks of treatment."

"Similarly, if you find that you have a big reduction in CRPS symptoms, please keep doing the treatment twice a day. However, if your symptoms get a lot worse during the course of the treatment period, please contact me using the contact details at the top of these instructions, because it might be that it would be better for you to stop doing the treatment early."

Explain when they should perform the first self-guided treatment session, which will be on the morning of the next day. ***Write this in their log book.*** *Also explain when they should perform the last self-guided treatment session, which should be the evening of the day before RS3.* ***Indicate the date and time of their last session in their log book.***

"Before we finish, I want to remind you that Monika [MH] should not know what treatment group you are in. For this reason, it is very important that you seal the goggles back in this bag before you return the goggles to her at the next treatment session so that she won't see what they look like."

Check if the person has any more questions. Give them the goggles sealed inside the bag.

Text S3. Data preparation

Participant-level data from the spatially-defined motor function task was processed to remove invalid trials. These included trials in which the movement endpoint did not match target location, the movement was initiated before target onset, or the screen touch time was not recorded (the latter type of invalid trials was only removed for movement execution times). Across all participants, both hands used, and all research sessions, 4.60% and 7.85% of all completed trials was removed for further processing of movement initiation and execution times, respectively. Movement initiation and execution times that were 3 SDs above or below individual participant's mean for each task condition (i.e. each combination of movement time measure, hand used, hand starting position, and visual field) were identified as participant-level outliers and replaced with the nearest non-outlier value (1.01% and 0.50%, respectively). If the number of invalid trials per task condition exceeded 3 *SDs* of a total group mean of invalid trials for that condition, we excluded participant's data from further analysis of this task. This meant that we could not obtain the complete set of the indices of directional hypokinesia or bradykinesia for some participants (8% of all possible indices). Any missing logbook ratings of pain, interference, and range of movement were interpolated using linear regression, except for two participants who dropped out and did not return their logbooks. Participants who withdrew following treatment allocation and did not return their treatment logbooks (PA treatment n = 2, Sham treatment n = 1) were assumed not to have completed any treatment sessions (thus their number of logged treatment sessions was entered as zero).

Reaction times 3 *SDs* above or below participant's mean for each condition of the Hand Laterality Recognition task (i.e. each combination of depicted hand and VF) were identified as participant-level outliers and replaced with the nearest non-outlier value (0.69% of trials across all participants and research sessions).

Participant scores on the self-report questionnaires, clinical assessments, and computer-based tasks that were 3 *SDs* above or below the mean scores of their relevant treatment group were identified as group-level outliers and replaced with the nearest non-outlier value (0.98% of data points across all measures and sessions).

Text S4. Factors excluded from exploratory best subsets regression analyses

We removed one influential observation from the analysis of change in pain intensity but retained all observations for the analysis on change in CRPS severity. The pool of potential predictors was limited by excluding factors that were nor linearly related with each outcome. For both change in pain intensity and CRPS severity score, we excluded baseline CRPS severity score, MDT ratio,

MPT ratio, and PSE (Landmark task). For change in pain intensity, we additionally excluded baseline PSS (TOJ task). We further identified predictors that were highly correlated with each other ($r > 0.70$), and excluded one of each pair, keeping the predictor that had higher correlation with each outcome. This was the case for the following pairs of predictors: grip strength ratio and ΔFTP ratio, current pain intensity and BPI pain severity, and BPI pain severity and BPI pain interference. We excluded grip strength ratio and BPI pain severity from the analysis of change in pain intensity, and ΔFTP ratio and BPI pain severity from the analysis of change in CRPS severity. Moreover, as there were two indices of directional hypokinesia and bradykinesia for each hand, we excluded one index of each pair which had lower correlation with each outcome. Thus, for the analysis of change in pain intensity, we excluded Index A of directional hypokinesia for the affected hand, and Index B for the unaffected hand, as well as Index B of directional bradykinesia for the affected hand, and Index B for the unaffected hand. For the analysis of change in CRPS severity, we excluded Index B of directional hypokinesia with the affected hand, and Index A for the unaffected hand, as well as Index B of directional bradykinesia for the affected hand, and Index A for the unaffected hand. Following these exclusions, variance inflation factors were < 5 for all best subsets fits.

Text S5. Daily logbook analysis: number of days to reach peak improvement and return to baseline during the treatment period

For daily pain intensity, median number of days from the beginning of treatment to reach peak improvement was 5 in PA group and 4.5 in sham treatment group. However, six participants in PA group and two participants in sham treatment group did not improve throughout the treatment period. Median number of days from peak improvement to return to baseline was 2.5 in PA group and 3 in sham treatment group. Two participants in each group did not return to their baseline average pain intensity throughout the treatment period or four weeks follow-up period.

For daily ratings of symptoms interference, median number of days to reach peak improvement was 4.5 in PA group and 4 in sham treatment group. However, four participants in PA group and eight participants in sham treatment group did not improve. Median number of days to return to baseline was 2 in PA group and 3.5 in sham treatment group. Five participants in PA group and four participants in sham treatment group did not return to their baseline symptoms interference.

For daily ratings of range of movement, median number of days to reach peak improvement was 6.5 in PA group, and 5 in sham treatment group. However, eight participants in PA group and 12 participants in sham group did not improve. Median number of days to return to baseline was 3 for both treatment groups. Two participants in PA group and three participants in sham group did not return to their baseline range of movement.

Text S6. Per-protocol analysis

Per-protocol population consisted of participants who completed their allocated treatment according to the trained protocol and missed no more than six retreatment sessions; and completed the primary outcome measures in RS1-RS4 (n = 41) and LTFU1 and LTFU2 (n = 37).

1. Participant characteristics

Table S3 presents baseline characteristics and comparisons between PA and sham treatment groups. The two groups were matched on the minimisation factors. They were also matched on baseline mean levels of optimism, mood disturbance, fear of movement, and expectations and criteria for success of the treatment (there were no significant differences between PA and sham treatment groups on any of the PCOQ items, Us ≥ 140.00, ps_{adj} ≥ .107, ds ≤ 0.60). Median number of logged treatment sessions did not significantly differ between the PA and sham treatment groups, indicating that they had similar extent of exposure to treatment.

2. Effects of PA treatment on the primary outcomes

We conducted a 2 (Group: PA, sham treatment) x 6 (Time: RS1-RS4, LTFU1-LTFU2) ANOVA on the primary outcome of current pain intensity (see Figure S4a). Significant main effect of Time, $F(5, 175) = 2.46$, $p = .035$, $\eta^2_p = 0.07$, suggested overall reduction in pain intensity (regardless of treatment) from RS2 (*Mdn* = 5.00, BCa 95% CI [5.00, 6.00]) to RS3 (*Mdn* = 5.00, BCa 95% CI [5.00, 6.00]). However, this effect did not withstand correction for multiple comparisons, $Zs \geq -1.77$, $ps_{adj} \geq .320$, $ds \leq 0.40$. There were no significant Group, $F(1, 35) = 0.02$, $p = .901$, $\eta^2_p < 0.01$, or interaction effects, $F(5, 175) = 0.68$, $p = .638$, $\eta^2_p = 0.02$. Effect size of the difference in mean change in pain intensity over the treatment period (RS3-RS2) between the PA and sham treatment groups was small, d = 0.38, 95% CI [-0.24, 1.00]. Mean pain reduction in the PA treatment group was -0.86 points on 0-10 NRS scale, BCa 95% CI [-1.89, -0.09]. In the sham treatment group, mean pain reduction was -0.20 points, BCa 95% CI [-0.89, 0.44].

A 2 (Group: PA, sham treatment) x 4 (Time: RS1-RS4) ANOVA on the primary outcome of CRPS severity score (see Figure S4b) revealed a significant main effect of Time, $F(2.29, 163.45) = 19.73$, $p < .001$, $\eta^2_p = 0.34$. Follow-up contrasts indicated overall reduction in CRPS severity (regardless of treatment) from RS2 (*Mdn* = 12.00, BCa 95% CI [12.00, 12.00]) to RS3 (*Mdn* = 11.00, BCa 95% CI [10.00, 11.00]), $Z = -3.91$, $p_{adj} = .002$, $d = 0.96$, which was maintained in RS4 (*Mdn* = 11.00, BCa 95% CI [10.00, 11.00]), $Z = -3.70$, $p_{adj} = .002$, $d = 0.90$. There were no significant differences between the remaining time points, $Zs \geq -1.85$, $ps_{adj} \geq .122$, $ds \leq 0.42$. There were no significant Group, $F(1, 39) = 0.11$, $p = .746$, $\eta^2_p < 0.01$, or interaction effects, $F(2.29, 163.45) = 0.35$, $p = .738$, $\eta^2_p = 0.01$. Effect size of the difference in mean change in CRPS severity over the treatment period (RS3-RS2) between the PA and sham treatment groups was small, d = -0.28, 95% CI [-0.89, 0.34]. Mean CRPS severity reduction in the PA treatment group

was -0.86 points on 0-16 scale, BCa 95% CI [-1.27, -0.41]. In the sham treatment group, mean CRPS severity reduction was -1.25 points, BCa 95% CI [-2.05, -0.48].

Individual pain and CRPS severity reduction scores over the treatment period are illustrated in Figure S5. Five participants in the PA group and four in the sham group achieved clinically significant reductions in pain (i.e. at least two-point decrease on 0-10 NRS scale [1]). None of the participants achieved clinically significant reduction in CRPS severity (i.e. at least 4.9 points decrease on 0-16 scale) [4].

3. Effects of PA treatment on the secondary outcomes

Group average scores on the self-report questionnaires, clinical assessments, and experimental tests of neuropsychological functions across all time points are reported in Table S4.

3.1. Self-reported pain, body representation, and emotional functioning

We conducted a series of 2 (Group: PA, sham treatment) x 6 (Time: RS1-RS4, LTFU1-LTFU2) ANOVAs on self-reported pain, body representation, and emotional functioning to test the effects of PA on these secondary outcomes. Results are reported in Table S5. A significant main effect of Time on pain interference (BPI) indicated that regardless of treatment, participants reported less interference from RS2 (*Mdn* = 6.00, BCa 95% CI [5.42, 6.71]) to RS3 (*Mdn* = 5.29, BCa 95% CI [4.57, 5.86]), and to RS4 (*Mdn* = 5.14, BCa 95% CI [4.00, 6.14]). However, these effects did not withstand correction for multiple comparisons, $Zs \geq -2.57$, $ps_{adj} \geq .080$, $ds \leq 0.59$. There was also a significant main effect of Time for neuropathic features of pain (PDQ). Regardless of treatment, participants reported decreased neuropathic component of pain from RS1 (*Mdn* = 25.00, BCa 95% CI [22.00, 26.00]) to RS2 (*Mdn* = 24.00, BCa 95% CI [24.00, 24.00]), and from RS3 (*Mdn* = 23.00, BCa 95% CI [21.00, 26.00]) to RS4 (*Mdn* = 22.00, BCa 95% CI [19.00, 25.00]). However, these effects did not withstand correction for multiple comparisons, $Zs \geq -2.08$, $ps_{adj} \geq .288$, $ds \leq 0.47$. ANOVA on body representation (BPDS) also revealed a significant main effect of Time. Despite participants reporting reduction in body perception disturbance from RS2 (*M* = 27.95, BCa 95% CI [24.63, 31.28]) to RS3 (*M* = 25.22, BCa 95% CI [21.22, 29.20]) and to RS4 (*M* = 25.46, BCa 95% CI [21.68, 29.02]), regardless of treatment, these effects were not sufficiently large to withstand correction for multiple comparisons, $ts \leq 2.30$, $ps_{adj} \geq .288$, $ds \leq 0.48$. We found a significant main effect of Time on fear of movement (TSK), suggesting that regardless of treatment, participants reported less fear of movement from RS2 (*M* = 38.49, BCa 95% CI [35.85, 41.48]) to RS3 (*M* = 37.05, BCa 95% CI [34.39, 39.81]) and to RS4 (*M* = 36.68, BCa 95% CI [34.07, 39.61]). However, these effects did not withstand correction for multiple comparisons, $ts \leq 2.56$, $ps_{adj} \geq .144$, $ds \leq 0.35$. There was also a significant interaction between Time and Group, indicating that sham treatment group reported decrease in fear of movement from RS2 to RS3, which was maintained in RS4 and LTFU2 (see Table S4). However, these effects also did not withstand correction for multiple comparisons, and there were no other

changes in either treatment group, $ts \leq 2.76$, $ps_{adj} \geq .192$, $ds \leq 0.73$. Our analyses did not reveal any other significant main effects or interactions on self-reported pain, body representation, or emotional functioning.

We also investigated whether PA affected participants' global impression of change due to treatment. A 2 (Group: PA, sham treatment) x 4 (Time: RS3, RS4, LTFU1, LTFU2) ANOVA did not reveal any significant main effects or interactions (see Table S5).

We performed a series of *t*-tests on the daily logbook ratings. PA and sham treatment groups did not differ on average daily ratings of pain intensity ($ts(39) \leq 1.75$, $ps \geq .071$, $ds \leq 0.58$), symptoms interference ($ts(39) \leq 1.44$, $ps \geq .158$, $ds \leq 0.45$), or range of movement ($ts(39) \leq 1.19$, $ps \geq .242$, $ds \leq 0.37$) at any time point during the first 10 weeks of the trial.

3.2. Sensory, motor, and autonomic functions

We performed a series of 2 (Group: PA, sham treatment) x 4 (Time: RS1-RS4) ANOVAs on allodynia ratings on the affected limb, two-point discrimination threshold ratios, absolute temperature and oedema differences between the two arms, and grip strength ratios. The results are reported in Table S5. Upon these clinical assessments, we only found a significant main effect of time on grip strength ratios. That is, regardless of treatment, participants' grip strength in the affected relative to unaffected hand improved from RS2 (*Mdn* = 0.31, BCa 95% CI [0.21, 0.41]) to RS3 (*Mdn* = 0.42, BCa 95% CI [0.33, 0.46]), $Z = -2.26$, $p_{adj} = .032$, $d = 0.52$. There were no significant differences between the remaining time points, $Zs \geq -1.92$, $ps_{adj} \geq .159$, $ds \leq 0.43$.

The Mechanical Detection Threshold, Mechanical Pain Threshold, and delta finger-to-palm distance ratios data were analysed using linear mixed models due to severe violations of normality, homogeneity of covariance, and/or sphericity assumptions. The results are reported in Table S6. There were no significant main effects or interactions on these outcomes.

3.3. Neuropsychological functions

We conducted a series of 2 (Group: PA, sham treatment) x 4 (Time: RS1-RS4) ANOVAs on the scores from test of neuropsychological functions, that is, visuospatial attention (Temporal Order Judgement and Greyscales tasks), mental representation of space (MNLB task), and body representation (Hand Laterality Recognition task). The results are reported in Table S5. We found a significant main effect of Time on the Hand Laterality Recognition accuracy index. Regardless of treatment, participants' accuracy in recognising images of unaffected relative to affected hands increased from RS2 (*M* = -2.93, BCa 95% CI [-5.56, -0.59]) to RS3 (*M* = 2.68, BCa 95% CI [0.15, 537]), $t(40) = -2.55$, $p_{adj} = .036$, $d = 0.40$, and this increase was maintained in RS4 (*M* = 1.95, BCa 95% CI [-1.17,4.98]), $t(40) = -2.58$, $p_{adj} = .039$, $d = 0.46$. There were no significant differences between the remaining time points, $ts \leq 1.43$, $ps_{adj} \geq .314$, $ds \leq 0.19$. This finding suggests an overall increased impairment of the representation of the affected hand over the

treatment period, as positive indices represent less accurate recognition of the images depicting affected hands.

The Landmark task and spatially-defined motor function task data were analysed using linear mixed models due to severe violations of normality, homogeneity of variance, and/or sphericity assumptions. The results are reported in Table S6. We found a significant main effect of Time on Index A of directional hypokinesia when participants used their affected hand. Regardless of treatment, participants became faster to initiate movements directed towards their affected relative to unaffected side from RS2 (*Mdn* = 11.24, BCa 95% CI [-31.99, 20.28]) to RS3 (*Mdn* = -23.63, BCa 95% CI [-46.40, -14.89]), Z = -2.24, p_{adj} = .040, d = 0.60. There were no significant differences between the remaining time points, $Zs \geq$ -0.94, $ps_{adj} \geq .240$, $ds \leq 0.24$. This suggests an overall reduction in directional hypokinesia over the treatment period. However, this effect was not evidenced on any other indices of directional hypokinesia or bradykinesia.

We found no other significant main effects of interactions on the tests of visuospatial attention, mental representation of space, spatially-defined motor function, or body representation.

4. Per-protocol versus intention-to-treat analysis

The results of per-protocol (PP) analysis were largely consistent with those of intention-to-treat (ITT) analysis in that there were no significant effects of PA on the primary or secondary outcomes. That is, we did not find any significant interactions between Time and treatment Group, which would yield significant differences following the corrections for multiple comparisons. Furthermore, overall (regardless of received treatment) reduction in CRPS severity over the treatment period, maintained four weeks later, was consistent between PP and ITT analyses. Overall reduction in self-reported pain interference over the treatment period (ITT) did not withstand correction for multiple comparisons in PP analysis. PP analysis revealed a significant overall improvement in grip strength of the affected relative to unaffected limb over the treatment period, which was not found in ITT analysis. Similarly, only PP analysis showed a significant overall change in hand laterality recognition accuracy over the treatment period, maintained four weeks later. Contrary to our hypothesis, this effect suggested greater impairment in representation of the affected limb following treatment period. Index A of directional hypokinesia when using the affected hand decreased over the treatment period, suggesting overall reduction of spatially-defined motor deficit over the treatment period, only in PP analysis. Overall slowing on Index B of directional bradykinesia when using the unaffected hand in PA group compared to sham treatment group found in ITT analysis, was not present in PP analysis. The above effects occurred regardless of PA or sham treatment.

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Supplemental figures

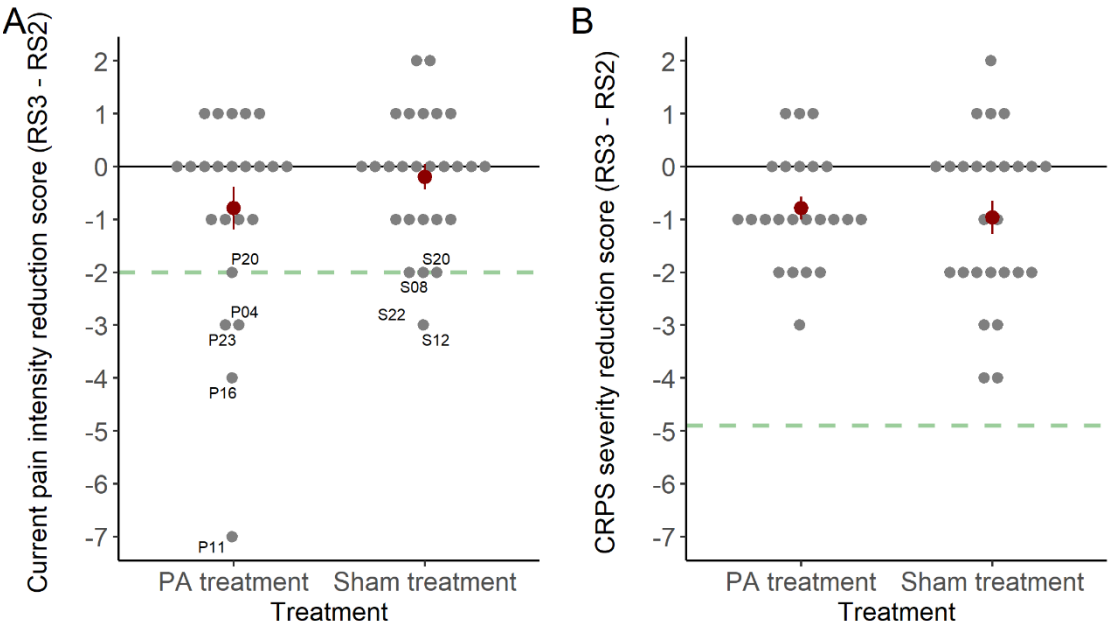

Figure S1. Individual pain intensity and CRPS severity reduction scores (intention-to-treat analysis). Grey circles represent individual participants' change on the primary outcomes of pain intensity (A) and CRPS severity (B) from immediately before treatment (RS2, research session 2) to immediately after treatment (RS3, research session 3). Negative scores indicate reduction in pain or CPRS severity over the treatment period. Red circles represent mean (95% CI) reduction scores in prism adaptation (PA) and sham treatment groups. Green dashed lines represent the threshold of clinically significant reduction in pain and CPRS severity and labels represent IDs of participants who achieved that reduction (see Table S1).

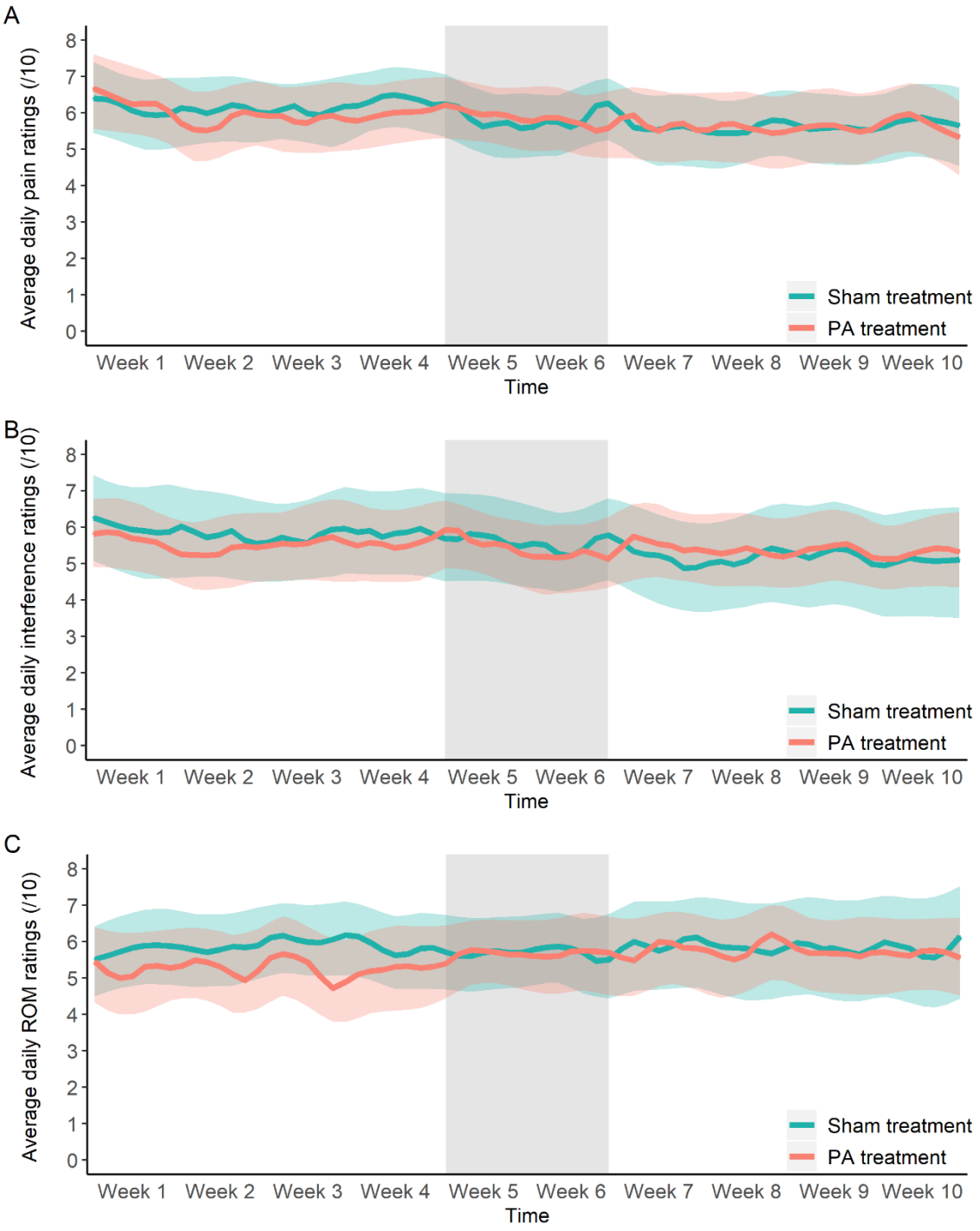

Figure S2. Daily logbook ratings (intention-to-treat analysis). Mean ratings of average daily pain intensity (A), symptom interference (B), and range of movement (C) in prism adaptation (PA; orange line) and sham treatment (blue line) group throughout the first 10 weeks of the study. Higher scores indicate greater pain intensity, greater symptoms interference, and better range of movement of the affected limb. Shaded areas around the lines represent BCa 95% CIs. Grey shaded rectangles represent the treatment period.

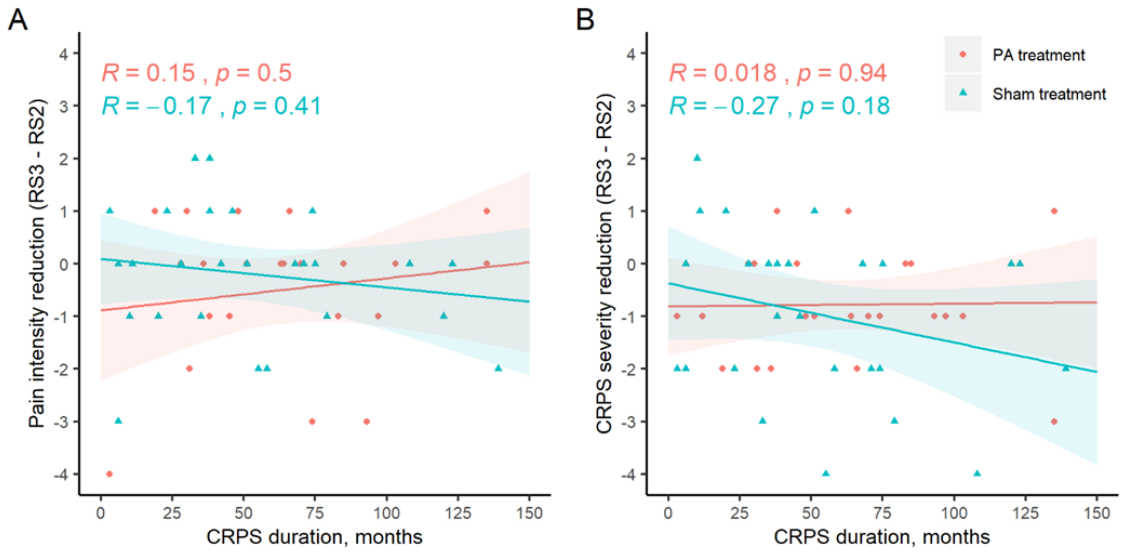

Figure S3. Scatterplots of changes on the primary outcomes vs. CRPS duration (intention-to-treat analysis). Relationships between individual participants' change in pain intensity (A) and CRPS severity (B) over the treatment period (between RS2, research session 2, and RS3, research session 3) and participants' disease duration (months since diagnosis) at the time of research session 1 are illustrated. Negative scores for pain and CRPS severity indicate reduction of these outcomes (i.e. improvement). Participants in the PA (prism adaptation) group are represented by orange circles, and those in the sham treatment group are represented by blue triangles. Lines of best fit with confidence intervals (shaded surfaces) are superimposed for each treatment group. *R*, Pearson's correlation coefficients for the relationships between pain reduction and disease duration (A) and CRPS severity reduction and disease duration (B). For pain reduction score, one observation was removed as an outlier (score = -7).

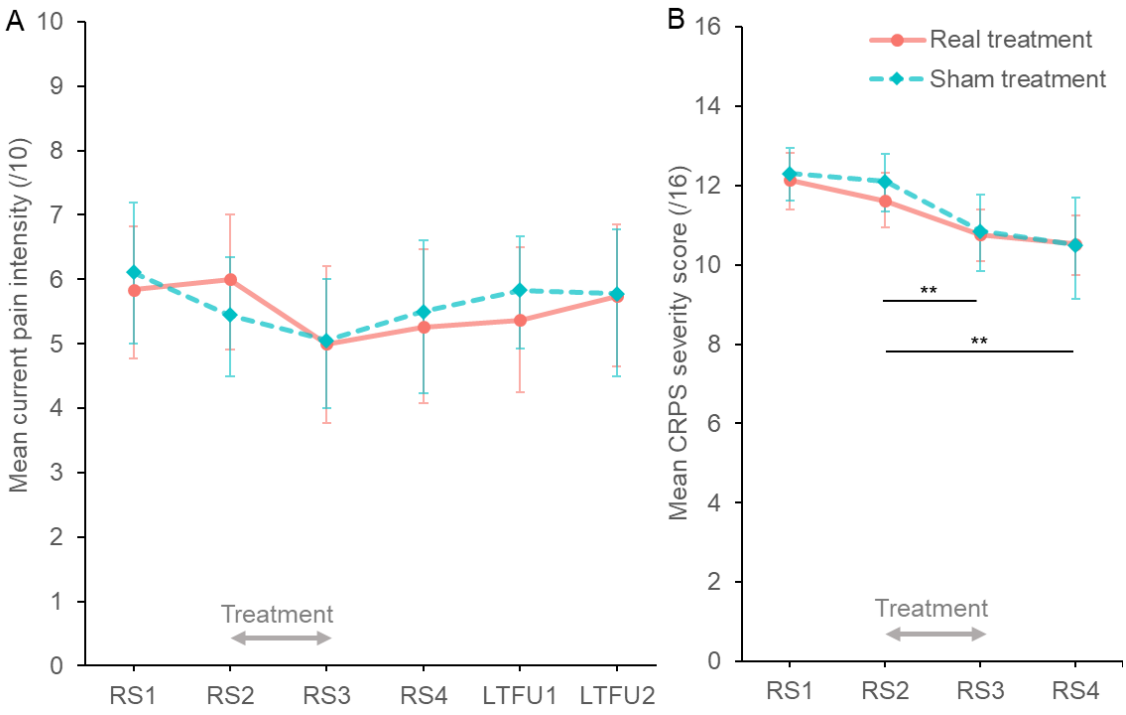

Figure S4. Primary outcomes (per-protocol analysis). Mean [BCa 95% CI] current pain intensity (A) and CRPS severity scores (B) in prism adaptation (PA; orange circles) and sham treatment (blue diamonds) groups in each time point. RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4; LTFU1 and LTFU2, long-term follow-up 1 and 2. Grey arrow represents treatment period. ** $p_{adj} < .01$.

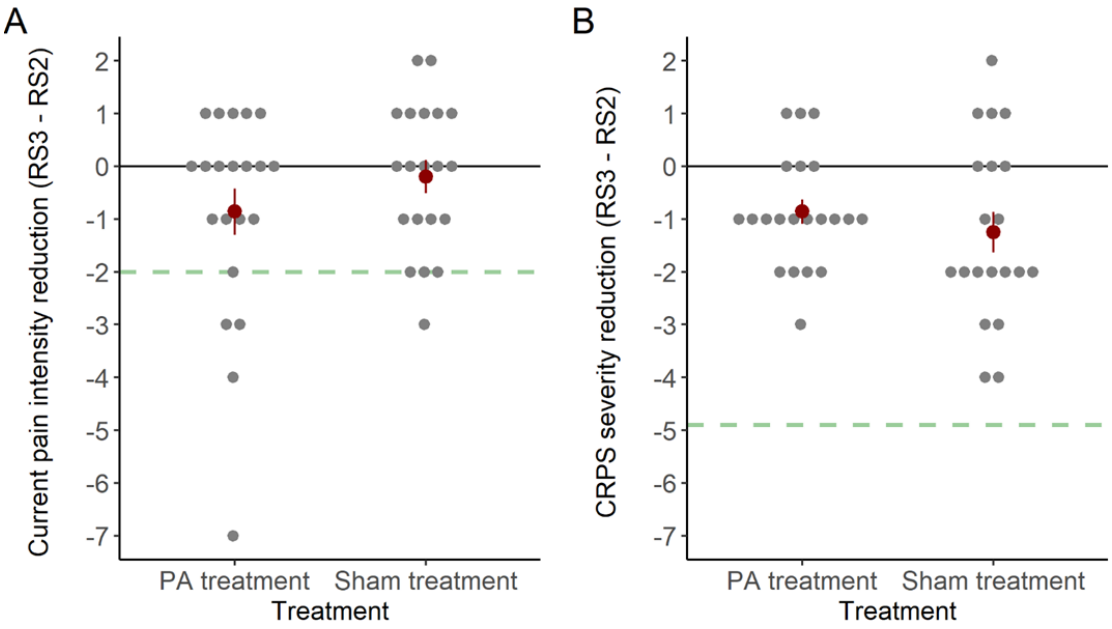

Figure S5. Individual pain intensity and CRPS severity reduction scores (per-protocol analysis). Grey circles represent individual participants' change on the primary outcomes of pain intensity (A) and CRPS severity (B) from immediately before treatment (RS2, research session 2) to immediately after treatment (RS3, research session 3). Negative scores indicate reduction in pain or CPRS severity over the treatment period. Red circle represents mean (95% CI) reduction scores in prism adaptation (PA) and sham treatment groups. Green dashed lines represent the threshold of clinically significant reduction in pain and CPRS severity.

Supplemental tables

Table S1 *Individual participant characteristics at baseline (RS1) and treatment exposure*

ID	Age / Sex / Handedness	CRPS limb	Inciting injury	Dur.	Pain	CSS	Current treatment / medication	Other pain	Other comorbidities	EHI pre-CRPS / ΔEHI	Treat.
P01	60 / M / R	L	Hand surgery	51	7	9	Aspirin, paracetamol*	-	Frozen joints, hypertension	100 / 0	29
P02	50 / F / R	L	Hand STI, shoulder surgery	45	7	13	Co-codamol, tramadol*, duloxetine, amitriptyline (LTFU2)‡	Fibromyalgia	Depression, IBS	100 / 0	29
P03†	36 / M / R	R	Finger & arm fracture	28	8	13	Morphine, pregabalin, baclofen, oramorph*, paracetamol*, ibuprofen*	-	Depression, anxiety	100 / -150	0
P04	63 / F / L	L	Arm fracture	74	4	9	Paracetamol, HT	Fibromyalgia	-	-100 / 0	29
P05	31 / F / R	L	Hand surgery	19	8	14	Amitriptyline, fluoxetine, gabapentin, codeine, tramadol*, paracetamol*, PT	Fibromyalgia	Asthma	80 / 20	29
P06	50 / F / R	R	Wrist sprain/crush	83	5	11	Ibuprofen, co-codamol, tramadol, amitriptyline (LTFU2)	CRPS NOS (L foot)	Asthma, Chronic Obstructive Pulmonary Disease, slipped disk	67 / -167	29
P07	39 / F / R	R	Finger STI	38	6	9	Paracetamol*, ibuprofen gel*, codeine*, meditation	Joints hypermobility, burning in hands and feet	Depression, vestibular dysfunction, postural orthostatic tachycardia	100 / -50	28
P08	37 / F / R	R	Finger STI	48	7	13	Naproxen, tramadol, pregabalin, amitriptyline, TENS, PT (stopped LTFU1)	-	Anxiety, depression, dyspraxia	100 / -117	27
P09	71 / F / R	R	Hand STI & surgery	66	2	11	Paracetamol*, co-codamol* (RS3; stopped RS4)	-	-	100 / -111	28
P10	54 / F / R	L	Finger fracture, wrist STI	210	10	13	Gabapentin, amitriptyline, naproxen*, morphine patch*	Frozen shoulder (L), hip pain (L), back pain	Psoriasis, depression, diabetes II, high blood pressure, perforated ear drum (L)	56 / 44	29
P11	52 / F / R	L	Wrist fracture, elbow fracture & surgery	12	6	14	Amitriptyline, paracetamol*, co-codamol* (stopped LTFU1)	-	-	29 / 38	29
P12	54 / F / R	L	Elbow fracture & surgery	63	7	12	PT, HT (stopped LTFU1)	-	-	60 / 40	29

ID	Age / Sex / Handedness	CRPS limb	Inciting injury	Dur.	Pain	CSS	Current treatment / medication	Other pain	Other comorbidities	EHI pre-CRPS / ΔEHI	Treat.
P13	40 / F / R	L	-	36	3	14	Gabapentin, nortriptyline, tramadol*, PT, co-codamol (RS3)	-	Endometriosis, polycystic ovaries, tachycardia	0 / 5	27
P14	36 / F / R	R	Wrist fracture	135	5	13	Pregabalin, duloxetine, co-codamol, PT, HT (stopped RS3)	-	-	62 / -22	28
P15	48 / F / R	R	Wrist surgery	64	7	11	Tramadol*, tapentadol*, SCS (off)	Migraines	Arthritis (back)	100 / -57	31
P16	58 / F / R	R	Wrist fracture	3	2	13	Amitriptyline, paracetamol, ibuprofen, PT	Chronic headaches	Arthritis (L knee), osteoporosis (R hand & L foot; RS3)	89 / -14	29
P17†	39 / F / R	L	-	85	7	12	Gabapentin, co-codamol, oxycodone, lidocaine patch*, ibuprofen gel*	Joints hypermobility	-	100 / 0	0
P18	49 / F / R	R	Wrist surgery	97	4	13	Oxycodone, naproxen, buprenorphine patch	-	Carpal tunnel syndrome (L wrist), depression, anxiety, diabetes	100 / -114	27
P19	59 / F / R	R	Wrist fracture	30	5	14	Paracetamol, lidocaine patch, HT	Hips pain	Asthma, hyperacusis	100 / -176	28
P20	38 / F / R	L	Shoulder whiplash injury	31	7	10	Amitriptyline, pregabalin, etoricoxib, duloxetine, HT, tai chi	Face & neck pain	Anxiety	100 / 0	29
P21	48 / F / R	L	Shoulder whiplash & STI	70	9	12	Duloxetine, ibuprofen, lidocaine patch, pregabalin, tramadol, SCS, PT	CRPS (legs)	Crohn's disease, depression, thyroidectomy	100 / 0	28
P22	24 / M / L	L	Finger STI	103	6	13	Nortriptyline	CRPS L leg	Depression	-43 / 116	27
P23	53 / M / R	R	Wrist fracture & surgery	93	5	14	Amitriptyline, pregabalin, co-codamol, tramadol, morphine, SCS, PT	-	-	100 / -200	29
S01	24 / F / R	R	Wrist sprain	42	8	15	Pregabalin, tramadol, duloxetine	Fibromyalgia	Depression, anxiety, diabetes, polycystic ovaries, asthma	100 / -120	28
S02†	54 / F / R	L	Arm fracture & surgery	6	8	13	-	-	Hypertension	40 / 60	15
S03	47 / M / R	R	Wrist fracture and surgery	38	7	13	Lidocaine patch, co-codamol	-	Prostate cancer (remission), depression, anxiety	100 / -200	25

ID	Age / Sex / Handedness	CRPS limb	Inciting injury	Dur.	Pain	CSS	Current treatment / medication	Other pain	Other comorbidities	EHI pre-CRPS / ΔEHI	Treat.
S04	31 / F / L	L	-	10	9	11	Naproxen, gabapentin, buprenorphine patch	Fibromyalgia, migraines	Asthma, polycystic ovaries	-100 / 50	28
S05	66 / M / R	R	Arm STI	108	6	11	Pregabalin, nortriptyline	-	-	100 / -20	29
S06	51 / F / R	L	Shoulder surgery	51	8	13	Gabapentin, ibuprofen, paracetamol, tapentadol* & zolmitriptan* (migraines)	Frozen shoulder (R), migraines	Osteopenia (back)	80 / 20	29
S07	51 / F / R	R	Hand fracture	23	3	13	Gabapentin (stopped LTFU2), amitriptyline, lidocaine patch, ibuprofen*, paracetamol*, stellate ganglion block, PT (RS3), pregabalin (LTFU2)	-	Asthma, IBS	100 / -180	29
S08	50 / F / R	R	-	55	3	12	Amitriptyline*, paracetamol*, mindfulness	-	Depression, hypothyroidism	100 / -114	29
S09	30 / F / R	R	Elbow fracture, wrist sprain & surgery	71	4	9	Gabapentin, meptazinol, ibuprofen*, pizotifen* (migraines; RS4)	Fibromyalgia, joints hypermobility, chronic headache, migraines	Anxiety, depression, Carpal tunnel syndrome (R wrist; RS2)	100 / 0	29
S10†	66 / F / R	L	Finger fracture	75	2	11	Co-codamol*, PT	-	-	100 / 0	8
S11	53 / F / R	R	Hand fracture	120	6	11	Ibuprofen*	-	Vertigo (RS4)	100 / -55	29
S12	36 / F / R	L	Finger & wrist STI	6	3	11	Gabapentin, PT, etoricoxib (RS2), ibuprofen* (LTFU1)	Fibromyalgia	Depression	100 / 0	29
S13	49 / F / R	L	Breast surgery	74	6	13	Gabapentin, fentanyl, baclofen, rizatriptan* (migraine), PT	Migraines	Depression	100 / 0	29
S14	73 / F / R	L	Arm STI	38	9	12	Buprenorphine, amitriptyline, aspirin, PT	Feet burning and spasms	Nails infections, hypothyroidism, PTSD, anxiety	100 / 0	29
S15†	28 / F / R	L	Elbow STI	35	6	13	None	Migraines	Depression, anxiety, epilepsy	27 / 73	23
S16	20 / F / R	R	Hand STI	11	5	14	Paracetamol (stopped RS4), OT (stopped LTFU1), co-codamol (RS4), pregabalin (LTFU2)	-	Asthma	80 / -140	29

ID	Age / Sex / Handedness	CRPS limb	Inciting injury	Dur.	Pain	CSS	Current treatment / medication	Other pain	Other comorbidities	EHI pre-CRPS / ΔEHI	Treat.
S17	25 / F / R	L	wrist sprain and laceration	46	6	13	Tramadol*	-	Depression, PTSD	44 / 45	28
S18†	72 / M / R	L	Heart surgery	123	8	12	Lidocaine patch*	-	Hernia surgery (recent), high blood pressure	100 / 0	8
S19	44 / F / R	R	Hand surgery	20	8	14	Gabapentin, amitriptyline	-	-	100 / -200	29
S20	67 / F / R	L	Arm fractures & surgery	139	7	13	Amitriptyline, gabapentin, duloxetine (stopped RS4), tapentadol	Peripheral neuropathy (L foot)	PTSD, depression, double vision, high blood pressure, anaemia, UTI, incontinence	100 / 0	29
S21†	41 / M / R	L	Shoulder dislocation	68	6	10	Amitriptyline, pregabalin, morphine*	CRPS (L leg, face)	IBS	100 / 0	29
S22	35 / F / L	L	Wrist sprain	58	8	11	Amitriptyline, pregabalin, co-codamol	-	-	-100 / 40	29
S23	37 / F / R	L	Wrist fracture	79	9	15	Amitriptyline, duloxetine, pregabalin, paracetamol, HT, tramadol* (RS2)	CRPS (L leg)	Fowler's syndrome	90 / 10	28
S24	37 / F / R	L	Shoulder dislocation & surgery	33	4	11	Morphine, paracetamol, TENS, PT, desensitization	Migraines	Polycystic ovaries	50 / 50	28
S25	47 / F / R	L	Wrist fracture	3	4	11	Lidocaine patch, naproxen (stopped RS4), PT, HT (stopped RS2), desensitisation	-	Hysterectomy; cholecystectomy	90 / 10	29
S26†	44 / F / R	L	Wrist sprain	28	7	13	Paracetamol* (RS2)	-	Bipolar disorder	-18 / 118	0

† Participant withdrew from the trial.

* Medication taken as needed.

‡ Time point in which a medication was introduced or stopped, or a new comorbidity reported, is specified in brackets where relevant.

ID, participant code (P, Prism Adaptation; S, Sham treatment); M, Male; F, Female; L, Left; R, Right; STI, soft tissue injury; Dur., CRPS duration in months since diagnosis; CSS, CRPS symptom severity score; RS2, RS3, and RS4, research sessions 2, 3, and 4; LTFU1 and LFTU2, long-term follow-ups 1 and 2; HT, hydrotherapy; PT, physiotherapy; TENS, transcutaneous electrical nerve stimulator; SCS, spinal cord stimulator; OT, occupational therapy; NOS, CRPS not otherwise specified; IBS, irritable bowel syndrome; PTSD, post-traumatic stress disorder; UTI, urinary tract infection; EHI pre-CRPS, recalled hand preference prior to CRPS onset (-100, extreme left-handedness; -40 – 40, ambidextrousness; 100, extreme right-handedness); ΔEHI, change in hand preference since CRPS onset (current – recalled pre-CRPS EHI); Treat., number of completed treatment sessions (/29).

Table S2 *Best subsets of factors (as measured in RS1) for predicting overall change in pain intensity and CRPS severity throughout the study period (intention-to-treat analysis)*

Best subsets models	Adj. R^2	AIC	CV
Change in pain intensity†			
Model 1: (+) Absolute change in handedness*	0.09	**-132.24**	**0.28**
Model 2: (+) Absolute change in handedness*, (+) Index A of directional bradykinesia for unaffected hand	0.13	-119.08	0.28
Model 3: (+) Oedema difference**, (-) Index B of directional hypokinesia for affected hand**, (-) Finger-to-palm distance ratio*	0.25	-105.79	0.30
Model 4: (+) Oedema difference**, (-) Index B of directional hypokinesia for affected hand*, (-) Finger-to-palm distance ratio*, (+) Mood disturbance	0.27	-105.68	0.29
Model 5: (+) Oedema difference**, (-) Index B of directional hypokinesia for affected hand**, (+) MNLB score*, (+) Absolute change in handedness, (-) Finger-to-palm distance ratio	0.32	-107.60	0.33
Change in CRPS severity†			
Model 1: (+) Current pain intensity**	0.13	-50.21	0.60
Model 2: (+) Current pain intensity**, (-) Index B of directional bradykinesia for unaffected hand*	0.23	-48.39	0.59
Model 3: (+) Current pain intensity***, (+) Oedema difference*, (+) Hand laterality recognition accuracy index*	0.25	**-55.52**	**0.55**
Model 4: (+) Allodynia on affected limb*, (-) Index B of directional bradykinesia for unaffected hand*, (-) Index B of directional hypokinesia for unaffected limb*, (+) disease duration	0.21	-45.66	0.58
Model 5: (-) Index B of directional bradykinesia for unaffected hand*, (-) Index B of directional hypokinesia for unaffected limb, (+) Allodynia on affected limb, (+) Disease duration, (+) Body perception disturbance score	0.21	-44.84	0.58

† Predicted outcomes were quantified as individual regression slopes based on pain intensity ratings throughout RS1-RS4 and LTFU1-LTFU2, and CRPS severity scores throughout RS1-RS4.

Asterisks indicate significant predictors: * $p < .05$, ** $p < .01$, *** $p < .001$; (+), positive predictor; (-), negative predictor.

Adj. R^2, adjusted R-squared; AIC, Akaike Information Criterion; CV, cross-validation error; MNLB, Mental Number Line Bisection;

Figures in bold indicate the lowest AIC and CV.

Table S3 *Baseline (RS1) participant characteristics by treatment group (per-protocol analysis)*

Measure	Prism adaptation treatment (n = 21)	Sham treatment (n = 20)	Contrast
Minimisation factors			
Current pain intensity (/10) *Mdn*	6.00 [5.00, 7.00]	6.00 [5.00, 8.00]	U = 189.00, p = .580, d = 0.17
CRPS severity score (/16) *Mdn*	13.00 [11.00, 14.00]	12.50 [11.00, 13.00]	U = 210.00, p = 1.00, d < 0.01
Primarily affected arm (% right)	48%	45%	$\chi^2(1)$ = .03, p = .876, ϕ = -0.03
Pre-CRPS dominant hand (% right)	91%	90%	$\chi^2(1)$ < .01, p = .959, ϕ = -0.01
Sex (% female)	86%	90%	$\chi^2(1)$ = .18, p = .675, ϕ = -0.07
Age (years) *M*	48.29 [43.00, 52.83]	43.65 [37.36, 50.39]	$t(39)$ = 1.14, p = .276, d = -0.35
CRPS in other body parts (% present)	14%	5%	$\chi^2(1)$ = 1.00, p = .317, ϕ = -0.16
Other non-CRPS pain (% present)	43%	45%	$\chi^2(1)$ = .02, p = .890, ϕ = -0.02
CRPS duration (months since diagnosis) *M*	61.71 [48.57, 75.91]	51.25 [34.72, 68.56]	$t(39)$ = 0.90, p = .397, d = -0.28
Other control measures			
Optimism (LOTR; /24) *M*	12.90 [10.89, 14.76]	11.70 [10.07, 13.27]	$t(39)$ = 0.94, p = .360, d = -0.29
Mood disturbance (POMS; /229) *M*	96.12 [80.01, 113.80]	84.80 [69.97, 100.30]	$t(39)$ = 0.91, p = .388, d = -0.28
Fear of movement (TSK; /68) *M*	38.34 [34.18, 42.62]	39.90 [36.36, 43.63]	$t(39)$ = -0.55, p = .578, d = 0.17
Number of logged treatment sessions (/29) *Mdn*	29.00 [28.56, 29.44]	29.00 [28.52, 29.48]	U = 184.50, p = .418, d = 0.21

LOTR, Revised Life Orientation Test; POMS, Profile of Mood States; TSK, Tampa Scale for Kinesiophobia.

Bootstrapped bias-corrected and accelerated 95% confidence intervals are reported in square brackets, [BCa 95% CI].

There were no significant differences between groups on any measures.

Table S4 *Mean or median values [BCa 95% CI] of self-reported; sensory, autonomic, and motor; and neuropsychological secondary outcome measures at each time point (per-protocol analysis)*

Measure	Treatment group	Time point					
		RS1	RS2	RS3	RS4	LTFU1	LTFU2
Self-report questionnaires							
Pain							
Pain severity (BPI; /10) *M*	PA	5.84 [4.88, 6.70]	6.01 [5.04, 6.91]	5.22 [4.15, 6.27]	5.34 [4.30, 6.41]	5.47 [4.38, 6.57]	5.49 [4.43, 6.53]
	Sham	5.72 [4.82, 6.53]	5.63 [4.65, 6.49]	5.49 [4.61, 6.27]	5.49 [4.26, 6.50]	5.75 [4.83, 6.57]	5.58 [4.36, 6.59]
Pain interference (BPI; /10) *Mdn*	PA	6.29 [5.71, 7.00]	6.29 [5.00, 7.29]	5.14 [2.57, 6.43]	5.14 [2.71, 6.71]	5.86 [2.50, 6.86]	5.71 [4.57, 6.57]
	Sham	5.79 [5.00, 6.86]	5.79 [3.81, 6.36]	5.36 [4.00, 6.29]	4.64 [3.43, 6.14]	5.14 [3.00, 6.57]	5.50 [3.14, 6.43]
Neuropathic features of pain (PDQ; /38) *Mdn*	PA	26.00 [26.00, 26.00]	24.00 [19.00, 26.00]	23.00 [19.00, 27.00]	22.00 [15.50, 27.00]	24.00 [16.00, 28.00]	24.00 [18.00, 28.00]
	Sham	23.50 [20.50, 28.00]	23.50 [19.00, 26.00]	22.50 [19.00, 26.50]	20.50 [14.00, 25.00]	21.00 [20.00, 24.00]	21.00 [17.00, 26.00]
Body representation							
Body perception disturbance (BPDS; /57) *M*	PA	27.95 [21.83, 35.18]	27.21 [22.22, 31.85]	20.79 [15.15, 26.95]	23.74 [19.09, 29.00]	24.63 [20.12, 29.81]	23.32 [18.98, 28.62]
	Sham	27.89 [21.83, 34.07]	27.61 [20.82, 34.30]	27.83 [21.56, 34.14]	25.72 [18.59, 32.37]	26.22 [20.50, 31.74]	26.89 [21.31, 32.56]
Emotional functioning							
Fear of movement (TSK; /68) *M*	PA	38.43 [33.82, 43.05]	38.11 [33.57, 42.82]	37.11 [33.01, 41.26]	37.79 [32.94, 42.45]	38.32 [33.56, 43.16]	39.95 [34.65, 44.90]
	Sham	39.44 [36.17, 42.72]	38.00 [34.75, 41.29]	35.94 [32.64, 39.31]	34.50 [30.78, 37.90]	35.85 [32.17, 39.41]	34.33 [30.58, 37.85]
Mood disturbance (POMS; /229) *Mdn*	PA	105.00 [91.00, 108.00]	107.80 [75.00, 110.00]	95.00 [69.00, 107.00]	94.00 [63.00, 105.00]	86.00 [58.00, 112.50]	84.00 [58.89, 118.00]
	Sham	68.00 [58.00, 80.00]	84.00 [64.00, 113.00]	69.50 [60.50, 85.34]	78.00 [51.00, 90.00]	74.50 [49.00, 91.00]	82.64 [48.00, 102.00]
Perceived improvement due to treatment							
Patient's global impression of change (PGIC; /7) *Mdn*	PA	-	-	2.00 [2.00, 4.00]	3.00 [3.00, 3.00]	2.00 [2.00, 4.00]	3.00 [2.00, 3.00]
	Sham	-	-	2.00 [1.00, 5.00]	3.00 [1.00, 5.00]	2.00 [1.50, 2.00]	2.00 [1.00, 4.00]

Measure	Treatment group	Time point					
		RS1	RS2	RS3	RS4	LTFU1	LTFU2
Clinical assessments							
Sensory functions							
Mechanical Detection Threshold ratio *Mdn*	PA	-0.04 [-0.67, 0.25]	-0.35 [-0.80, -0.13]	-0.44 [-0.76, -0.10]	-0.54 [-1.89, -0.10]	-	-
	Sham	-0.30 [-1.37, 0.62]	0.00 [-0.35, 0.17]	-0.27 [-1.19, 0.31]	-0.46 [-1.24, 0.45]	-	-
Mechanical Pain Threshold ratio *Mdn*	PA	0.62 [0.00, 0.69]	0.50 [0.43, 0.53]	0.07 [-0.32, 0.69]	0.50 [0.13, 0.69]	-	-
	Sham	0.58 [0.24, 0.67]	0.59 [0.44, 0.75]	0.61 [0.34, 0.84]	0.50 [0.26, 0.78]	-	-
Allodynia (affected; /100) *Mdn*	PA	14.00 [8.07, 26.67]	18.87 [4.33, 30.89]	16.90 [7.40, 26.67]	10.73 [2.53, 18.00]	-	-
	Sham	25.83 [8.36, 41.00]	14.67 [4.33, 32.00]	21.00 [2.27, 65.67]	25.00 [5.23, 52.00]	-	-
Two-Point Discrimination Threshold ratio *M*	PA	-0.05 [-0.24, 0.14]	-0.04 [-0.20, 0.11]	-0.19 [-0.39, 0.00]	-0.09 [-0.27, 0.09]	-	-
	Sham	0.11 [-0.05, 0.26]	0.00 [-0.20, 0.16]	0.03 [-0.14, 0.20]	0.08 [-0.14, 0.29]	-	-
Autonomic functions							
Absolut temperature difference (°C) *Mdn*	PA	0.57 [0.30, 1.43]	0.30 [0.13, 1.00]	0.47 [0.20, 0.73]	0.53 [0.17, 1.33]	-	-
	Sham	0.60 [0.25, 0.80]	0.72 [0.40, 1.10]	0.65 [0.40, 1.10]	0.43 [0.35, 0.83]	-	-
Oedema difference (cm) *M*	PA	0.04 [-0.40, 0.46]	-0.05 [-0.40, 0.27]	-0.22 [-0.66, 0.22]	-0.26 [-0.65, 0.12]	-	-
	Sham	-0.01 [-0.50, 0.57]	0.11 [-0.38, 0.63]	-0.01 [-0.52, 0.49]	0.19 [-0.27, 0.66]	-	-
Motor functions							
Grip strength ratio *Mdn*	PA	0.35 [0.18, 0.39]	0.31 [0.19, 0.44]	0.35 [0.30, 0.45]	0.39 [0.30, 0.46]	-	-
	Sham	0.28 [0.18, 0.66]	0.33 [0.14, 0.67]	0.44 [0.15, 0.81]	0.42 [0.16, 0.77]	-	-
Delta finger-to-palm distance ratio *Mdn*	PA	0.70 [0.62, 0.86]	0.67 [0.61, 0.84]	0.73 [0.63, 0.84]	0.79 [0.70, 0.82]	-	-
	Sham	0.85 [0.63, 0.92]	0.78 [0.42, 0.94]	0.88 [0.61, 0.92]	0.86 [0.64, 0.94]	-	-
Experimental tests of neuropsychological functions							
Visuospatial attention							
Temporal Order Judgement task (PSS; ms) *Mdn*	PA	-9.77 [-14.38, 5.52]	-3.76 [-14.83, 8.35]	-3.26 [-8.75, 11.16]	5.18 [-7.84, 20.27]	-	-
	Sham	-2.42 [-7.40, 7.06]	-0.75 [-8.33, 9.15]	1.17 [-5.25, 9.56]	-2.12 [-10.48, 11.52]	-	-
Landmark task (PSE; °) *Mdn*	PA	-0.01 [-0.25, 0.42]	0.06 [-0.04, 0.21]	0.03 [-0.10, 0.48]	-0.03 [-0.14, 0.19]	-	-

Measure	Treatment group	Time point					
		RS1	RS2	RS3	RS4	LTFU1	LTFU2
	Sham	0.06 [-0.09, 0.27]	0.05 [-0.12, 0.15]	-0.05 [-0.11, 0.10]	0.02 [-0.04, 0.09]	-	-
Greyscales task *M*	PA	-0.22 [-0.40, -0.03]	-0.15 [-0.38, 0.07]	-0.11 [-0.33, 0.09]	-0.14 [-0.37, 0.07]	-	-
	Sham	-0.05 [-0.26, 0.17]	-0.02 [-0.21, 0.19]	0.05 [-0.13, 0.22]	-0.04 [-0.22, 0.16]	-	-
Mental representation of space							
Mental Number Line Bisection task *M*	PA	-0.04 [-0.91, 0.75]	0.03 [-0.62, 0.71]	-0.11 [-0.69, 0.49]	-0.01 [-0.51, 0.50]	-	-
	Sham	0.35 [-0.21, 0.98]	0.24 [-0.41, 0.89]	0.05 [-0.60, 0.74]	0.15 [-0.32, 0.73]	-	-
Spatially-defined motor function							
Directional hypokinesia, affected hand, Index A (MIT; ms) *Mdn*	PA	-18.41 [-76.15, 44.53]	16.76 [-25.16, 32.93]	-16.32 [-64.67, -13.44]	-21.56 [-43.19, -5.87]	-	-
	Sham	-4.59 [-25.43, 13.03]	4.98 [-40.87, 15.79]	-40.48 [-58.35, -2.88]	-13.03 [-40.85, 1.72]	-	-
Directional hypokinesia, affected hand, Index B (MIT; ms) *Mdn*	PA	-27.95 [-84.09, -16.84]	-25.41 [-84.04, 40.70]	-43.14 [-63.51, -24.62]	-4.40 [-30.32, 8.72]	-	-
	Sham	-33.37 [-47.11, 50.73]	-6.76 [-44.59, 9.61]	-20.29 [-60.27, 7.38]	11.04 [-45.35, 40.53]	-	-
Directional hypokinesia, unaffected hand, Index A (MIT; ms) *Mdn*	PA	-5.80 [-26.78, 37.64]	5.61 [-17.46, 22.06]	3.39 [-32.09, 22.88]	-12.38 [-52.41, 17.33]	-	-
	Sham	7.21 [-0.31, 24.74]	7.70 [-11.05, 14.27]	3.42 [-10.41, 18.35]	-0.44 [-13.70, 25.06]	-	-
Directional hypokinesia, unaffected hand, Index B (MIT; ms) *Mdn*	PA	-0.77 [-44.84, 24.96]	7.45 [-17.01, 25.19]	7.04 [-27.53, 33.20]	-3.72 [-26.43, 39.44]	-	-
	Sham	2.56 [-17.32, 12.76]	9.18 [-10.21, 26.22]	0.77 [-13.43, 24.11]	19.39 [-2.21, 38.21]	-	-
Directional bradykinesia, affected hand, Index A (MET; ms) *Mdn*	PA	48.04 [3.73, 245.60]	55.20 [-14.44, 176.32]	46.94 [7.88, 87.48]	50.15 [34.08, 107.84]	-	-
	Sham	81.14 [4.37, 108.44]	50.72 [5.28, 122.01]	31.79 [-0.20, 101.61]	33.37 [21.88, 55.57]	-	-
	PA	-15.38 [-62.78, 12.93]	-95.85 [-182.07, -12.52]	-80.19 [-123.73, -64.61]	-67.48 [-92.39, -36.36]	-	-

Measure	Treatment group	Time point					
		RS1	RS2	RS3	RS4	LTFU1	LTFU2
Directional bradykinesia, affected hand, Index B (MET; ms) *Mdn*	Sham	-96.11 [-195.76, -63.53]	-173.54 [-203.60, -28.19]	-81.52 [-146.50, -14.65]	-78.67 [-116.53, -58.59]	-	-
Directional bradykinesia, unaffected hand, Index A (MET; ms) *Mdn*	PA	106.75 [58.39, 122.06]	53.48 [21.61, 140.66]	81.27 [48.90, 100.58]	74.51 [37.54, 115.76]	-	-
	Sham	94.46 [75.44, 141.24]	83.44 [32.20, 143.56]	85.25 [68.35, 98.56]	56.18 [31.60, 67.12]	-	-
Directional bradykinesia, unaffected hand, Index B (MET; ms) *Mdn*	PA	44.75 [-46.27, 64.92]	39.66 [3.34, 54.94]	49.96 [28.52, 64.43]	16.71 [-12.88, 43.29]	-	-
	Sham	3.49 [-28.91, 37.31]	44.61 [-0.49, 64.77]	20.64 [-10.65, 48.57]	3.38 [-22.98, 12.57]	-	-
Body representation							
Hand laterality recognition Accuracy Index (%) *M*	PA	-2.67 [-5.89, 0.90]	-2.86 [-5.89, 0.02]	1.05 [-2.31, 4.41]	1.33 [-3.18, 5.65]	-	-
	Sham	2.50 [-3.00, 7.70]	-3.00 [-7.46, 0.83]	4.40 [-0.09, 8.93]	2.60 [-2.14, 7.56]	-	-
Hand laterality recognition Reaction Time Index (ms) *Mdn*	PA	-73.17 [-149.15, -6.80]	-99.42 [-321.06, 78.88]	-7.51 [-105.57, 91.93]	-84.89 [-191.84, -3.45]	-	-
	Sham	-45.78 [-153.70, 54.45]	-83.02 [-223.25, 14.50]	-87.71 [-240.98, 117.34]	18.54 [-123.40, 184.00]	-	-

BPI, Brief Pain Inventory; PDQ, Pain Detect Questionnaire; BPDS, Bath CRPS Body Perception Disturbance Scale; TSK, Tampa Scale for Kinesiophobia; POMS, Profile of Mood States; PSS, Point of Subjective Simultaneity; PSE, Point of Subjective Equality; MIT, movement initiation time; MET, movement execution time; PA, prism adaptation treatment; Sham, sham treatment; RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4; LTFU1 and LFTU2, long-term follow-ups 1 and 2.

Table S5 *Analysis of variance results for secondary outcome measures (per-protocol analysis)*

Measure	Effect	*df*†	*F*	*p*	η^2_p
Self-report questionnaires					
Pain severity (BPI)	Time	3.98, 139.33	1.50	0.205	0.04
	Group	1, 35	0.01	0.944	< 0.01
	Time x Group	3.98, 139.33	0.69	0.600	0.02
Pain interference (BPI)	Time*	3.24, 113.39	5.06	0.002	0.13
	Group	1, 35	0.15	0.702	< 0.01
	Time x Group	3.24, 113.39	0.83	0.489	0.02
Neuropathic features of pain (PDQ)	Time*	3.30, 115.47	4.20	0.006	0.11
	Group	1, 35	0.38	0.542	0.01
	Time x Group	3.30, 115.47	0.79	0.511	0.02
Body perception disturbance (BPDS)	Time*	3.42, 119.54	2.82	0.035	0.07
	Group	1, 35	0.43	0.515	0.01
	Time x Group	3.42, 119.54	2.15	0.089	0.06
Fear of movement (TSK)	Time*	3.90, 136.61	3.02	0.021	0.08
	Group	1, 35	0.45	0.507	0.01
	Time x Group*	3.90, 136.61	4.08	0.004	0.10
Mood disturbance (POMS)	Time	3.57, 125.02	2.47	0.055	0.07
	Group	1, 35	1.18	0.284	0.03
	Time x Group	3.57, 125.02	0.27	0.881	0.01
Patient's global impression of change (PGIC)	Time	3, 105	0.64	0.588	0.02
	Group	1, 35	< 0.01	0.988	< 0.01
	Time x Group	3, 105	0.38	0.765	0.01
Clinical assessments					
Allodynia (affected limb)	Time	2.14, 83.43	1.13	0.332	0.03
	Group	1, 39	0.84	0.366	0.02
	Time x Group	2.14, 83.43	0.57	0.576	0.01
Two-Point Discrimination Threshold ratio	Time	3, 117	1.07	0.364	0.03
	Group	1, 39	1.81	0.186	0.04
	Time x Group	3, 117	0.80	0.499	0.02
Absolut temperature difference	Time	3, 117	0.66	0.577	0.02
	Group	1, 39	0.01	0.913	< 0.01
	Time x Group	3, 117	0.33	0.802	0.01
Oedema difference	Time	2.54, 99.16	1.12	0.339	0.03
	Group	1, 39	0.40	0.531	0.01
	Time x Group	2.54, 99.16	2.64	0.063	0.06
Grip strength ratio	Time*	2.36, 92.03	4.43	0.010	0.10
	Group	1, 39	0.28	0.599	0.01
	Time x Group	2.36, 92.03	0.78	0.479	0.02

Measure	Effect	*df*†	*F*	*p*	η^2_p
Experimental tests of neuropsychological functions					
Temporal Order Judgement task (PSS)	Time	1.74, 67.97	1.75	0.186	0.04
	Group	1, 39	0.35	0.556	0.01
	Time x Group	1.74, 67.97	0.73	0.466	0.02
Greyscales task	Time	3, 117	1.54	0.207	0.04
	Group	1, 39	0.97	0.330	0.02
	Time x Group	3, 117	0.15	0.927	< 0.01
Mental Number Line Bisection task	Time	2.41, 94.10	0.40	0.712	0.01
	Group	1, 39	0.30	0.586	0.01
	Time x Group	2.41, 94.10	0.16	0.885	< 0.01
Hand laterality recognition Accuracy Index	Time*	3, 117	2.71	0.049	0.06
	Group	1, 39	2.00	0.165	0.05
	Time x Group	3, 117	0.58	0.632	0.01
Hand laterality recognition Reaction Time Index	Time	3, 117	1.58	0.198	0.04
	Group	1, 39	0.87	0.357	0.02
	Time x Group	3, 117	0.47	0.702	0.01

* Statistically significant effect ($p < .05$).

† Greenhouse-Geisser adjusted degrees of freedom are reported where sphericity assumption was violated. BPI, Brief Pain Inventory; PDQ, Pain Detect Questionnaire; BPDS, Bath CRPS Body Perception Disturbance Scale; TSK, Tampa Scale for Kinesiophobia; POMS, Profile of Mood States. PSS, Point of Subjective Simultaneity.

Table S6 *The results of the bootstrapped linear mixed models regressions of scores on the tests of sensory and motor function, visuospatial attention, and spatially-defined motor function - directional hypokinesia and bradykinesia (per-protocol analysis)*

Model term	**Coefficient estimate [95% CI]**			
	Sensory functions		**Motor function**	**Visuospatial attention**
	Mechanical Detection Threshold ratio	**Mechanical Pain Threshold ratio**	**Delta finger-to-palm ratio**	**Landmark task (PSE)**
Intercept	-1.31 [-3.24, 0.31]	-0.09 [-0.89, 0.73]	0.70 [0.64, 0.75]*	0.25 [-1.28, 2.67]
Time (RS2 = 0)				
RS1	-2.81 [-8.37, 1.05]	-0.57 [-1.92, 0.46]	-0.04 [-0.12, 0.04]	2.72 [-0.23, 8.90]
RS3	-0.55 [-3.15, 1.66]	-0.66 [-1.99, 0.42]	-0.02 [-0.12, 0.05]	0.11 [-1.84, 2.16]
RS4	-1.66 [-5.21, 1.24]	0.17 [-0.68, 1.12]	0.02 [-0.06, 0.10]	0.24 [-1.79, 2.58]
Group (PA = 0)				
Sham	0.29 [-2.25, 2.80]	0.23 [-0.74, 1.20]	-0.01 [-0.09, 0.08]	-0.27 [-2.70, 1.23]
Time x Group (RS2, PA = 0)				
RS1, Sham	2.95 [-1.97, 8.99]	0.32 [-1.13, 1.89]	0.05 [-0.06, 0.17]	-2.53 [-8.79, 0.47]
RS3, Sham	-2.04 [-7.86, 2.51]	1.00 [-0.29, 2.47]	0.06 [-0.04, 0.19]	-0.09 [-2.13, 1.87]
RS4, Sham	1.95 [-1.92, 6.40]	-0.04 [-1.19, 1.10]	0.02 [-0.08, 0.13]	-0.24 [-2.57, 1.76]

Model term	Coefficient estimate [95% CI]							
	Directional hypokinesia (MIT)				Directional bradykinesia (MET)			
	Affected hand		Unaffected hand		Affected hand		Unaffected hand	
	Index A	Index B	Index A	Index B	Index A	Index B	Index A	Index B
Intercept	31.72 [-115.60, 136.20]	30.41 [-127.78, 174.97]	-27.48 [-94.91, 24.38]	-22.67 [-74.98, 21.53]	50.84 [-103.74, 169.43]	-116.48 [-188.02, -44.74]*	87.86 [55.03, 122.03]*	45.01 [13.52, 77.95]*
Time (RS2 = 0)								
RS1	-29.23 [-194.86, 121.55]	-40.50 [-241.18, 121.94]	41.87 [-22.44, 120.05]	12.49 [-50.71, 78.42]	-129.53 [-603.90, 164.88]	67.75 [-40.73, 192.13]	7.08 [-39.00, 50.36]	-33.52 [-99.06, 30.31]
RS3	-250.17 [-663.20, -5.27]*	-265.27 [-677.40, 5.61]	31.77 [-33.84, 122.10]	18.80 [-42.65, 90.16]	10.98 [-171.21, 162.96]	-6.82 [-108.75, 96.48]	-6.50 [-52.34, 34.75]	-2.43 [-40.59, 33.88]
RS4	-62.05 [-200.75, 52.76]	-42.62 [-228.78, 97.84]	1.82 [-70.40, 87.69]	22.41 [-37.17, 83.89]	23.73 [-134.83, 186.62]	51.90 [-41.76, 142.84]	-14.81 [-59.08, 25.21]	-27.16 [-71.17, 13.87]
Group (PA = 0)								
Sham	-43.75 [-150.14, 110.47]	-37.04 [-189.89, 118.58]	32.48 [-25.63, 104.72]	41.05 [-14.22, 108.37]	-3.16 [-131.20, 152.37]	25.69 [-74.31, 128.21]	-6.96 [-47.42, 33.73]	-24.73 [-68.42, 18.68]
Time x Group (RS2, PA = 0)								
RS1, Sham	30.79 [-126.93, 206.42]	52.40 [-115.17, 261.61]	-49.22 [-140.62, 32.79]	-52.67 [-161.06, 39.89]	143.71 [-161.33, 622.79]	-116.70 [-268.32, 43.71]	-0.74 [-63.40, 60.29]	17.87 [-61.55, 96.89]
RS3, Sham	246.39 [-6.06, 645.57]	251.56 [-21.01, 657.54]	-32.26 [-125.88, 41.88]	-32.33 [-111.24, 42.15]	-17.36 [-193.70, 167.19]	10.77 [-118.96, 148.00]	10.08 [-40.39, 59.93]	5.03 [-51.12, 59.11]
RS4, Sham	44.62 [-98.45, 202.44]	55.16 [-102.42, 258.32]	-4.74 [-98.42, 74.57]	-15.31 [-93.86, 66.73]	-26.95 [-189.23, 144.88]	-19.30 [-149.11, 109.53]	-10.53 [-58.80, 40.61]	4.72 [-46.91, 61.09]

* Significant effect (95% CI around the coefficient estimate does not include 0).

The reference condition for dummy variable coding is indicated within parentheses for each term.

PA, prism adaptation treatment; Sham, sham treatment; RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4; PSE, Point of Subjective Equality; MIT, movement initiation time; MET, movement execution time.

Table S7 *CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	230
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	231
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	232-233
	2b	Specific objectives or hypotheses	232-233
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	233
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	233
Participants	4a	Eligibility criteria for participants	234
	4b	Settings and locations where the data were collected	233
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	236-238, Figure 1
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	239-246, Figure 1
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Text S1
Sample size	7a	How sample size was determined	246
	7b	When applicable, explanation of any interim analyses and stopping guidelines	234
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	238
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	238
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	238
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	237-238
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	237-239
	11b	If relevant, description of the similarity of interventions	238

Section/Topic	Item No	Checklist item	Reported on page No
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	247-248
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	247-249
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	246-247, Figure 2
	13b	For each group, losses and exclusions after randomisation, together with reasons	246-247
Recruitment	14a	Dates defining the periods of recruitment and follow-up	233
	14b	Why the trial ended or was stopped	246-247
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	249-250, Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	251-263, Figure 4, Tables 2-7
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	264-268, Text S6
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Figure 2
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	271-272
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	268-272
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	268-272
Other information			
Registration	23	Registration number and name of trial registry	233
Protocol	24	Where the full trial protocol can be accessed, if available	233, Chapter 3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	272